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# OSTEODYSMETAMORPHOSIS FETALIS

## A CLINICAL-PATHOLOGICAL STUDY OF A CONGENITAL SKELETAL DISEASE WITH RETARDED GROWTH, HYPOPHOSPHATASEMIA AND RENAL DAMAGE*

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A LARGE number of congenital or acquired skeletal diseases have been described, many being syndromes, the interpretation of which is unsatisfactory. A reason for this may be that the symptoms of these conditions may vary considerably with the severity of the disorder, and that various constitutional factors may play a role. Another consideration is that bone tissue may react in different ways, according to the age at which a disease is first manifested. Osteogenesis imperfecta, osteopetrosis, and achondroplasia are disorders which may, from both clinical and pathological viewpoints, be regarded as well-defined syndromes. On the other hand, it is probable that a great number of other syndromes either may be reduced to a few delimited entities, or comprise combinations of more than one etiologically and pathogenetically distinct disease.

In this communication a report is given of a congenital skeletal disorder characterized by retarded growth with reduced rebuilding of bone tissue. With the aid of biophysical methods a thorough study of the properties of the organic and inorganic constituents of bone tissue and its ultrastructure has been performed. These studies have revealed a skeletal disease of a hitherto undescribed type. Apart from generalized skeletal disease, nephrocalcinosis with nephrocirrhosis was also present. In the light of the occurrence of a primary skeletal disease together with renal damage, the pathogenesis of combined skeletal and kidney diseases during infancy is discussed.

### METHOD

*Analytical Methods.*—Serum phosphate was determined according to Youngburg and Youngburg,[25] urinary phosphate according to Fiske and Subbarow,[13] serum calcium according to Biering,[3] and urinary calcium according to Kramer and Tisdall.[17] Total bases in the serum were determined electrolytically according to Broch.[4] Alkaline phosphatase activity in the serum was determined according to Buch and Buch.[5] According to this method, the normal activity throughout infancy was 10 to 20 units. The activity of alkaline phosphatase in bone tissue and in the kidneys was determined according to the same method after extraction of the enzyme.[20] The different protein com-

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ponents in serum were determined by paper electrophoresis. The excretion of amino acids in the urine was calculated from the determination of α-amino-nitrogen[23] excretion. The urinary amino acid pattern was studied by two-dimensional paper chromatography.[7]

*Techniques Applied on Bone Tissue.*—The tissue was fixed in absolute ethanol. Thin sections of bone tissue were cut out with a rotating saw with a very thin blade. The sections were ground on glass plates to a thickness of 50 to 100 micra.

*Microradiography.*—This method was applied to study the degree of mineralization and the distribution of mineral salts in different structures of the bone tissue. The method used in the microradiographic examination was chiefly that described by Engström and Wegstedt.[11] Some of the preparations have also been microradiographed with Philip's diffraction unit with a copper target. The tube was operated with 35 kV and 12 mA. The distance between focus and film was 25 cm. The specimens were placed in direct contact with the photographic emulsion, which was of fine-grain type with a resolving power of about 1 μ (Kodak spectroscopic plate No. 649). The microradiograms were enlarged by microphotography on Kodak 0250 plates.

*Autoradiographic Investigation of the Ion Exchange of the Mineral Salts in Vitro.*—The in vitro uptake of $Ca^{45}$ was studied by incubating the ground bone sections in $Ca^{45}Cl_2$-solution according to a method described earlier.[8] Agfa Printon film was used in the autoradiographic procedure.

*Investigation of the Ultrastructure of the Bone.*—This was performed with x-ray diffraction using a Hilger 190 mm. cylinder camera. The method was the same as that described earlier in similar investigations.[10]

*Examinations of the Collagen Pattern.*—The microradiographed bone sections were decalcified in formic acid and mounted in 5 per cent sodium sulfate. The sections were then microphotographed in transmitted and in polarized light (crossed Nicol prisms).

*Examination of the Deposition of Calcium Salts in the Kidneys.*—A procedure similar to that used in the investigation of the distribution of calcium salts in bone tissue was employed to illustrate the distribution of calcium salts in the kidneys. The cut sections were 200 μ in thickness. Microradiography was performed in the same way as with the bone tissue, though with a lower voltage (25 kV and 12 mA).

## CASE REPORT

Karolinska Sjukhuset Pediatric Clinic (Journal No. 52 10 02 C.N.).—The girl was the second child of healthy parents. The family history was not relevant. Birth weight was 4,200 grams. The delivery was normal. The infant was given mixed feeding for the first three months, thereafter cow's milk formula. Ever since birth she received about 1,000 units of vitamin D daily. Apart from a tendency to feed slowly from the breast or from the bottle she progressed satisfactorily until the age of 3 months. At this stage anorexia and vomiting started. The baby became hypotonic and flabby and ceased to gain weight. At the age of 5 months she was admitted to a children's hospital because of vomiting, general muscle hypotonia, and bulging fontanel. Weight on admission was 5,800 grams. The examination revealed that the child had a general

skeletal disease resembling rickets, and symptoms of a renal lesion. After one month's observation, during which time there was no improvement, the child was transferred to the Children's Clinic at Karolinska Sjukhuset.*

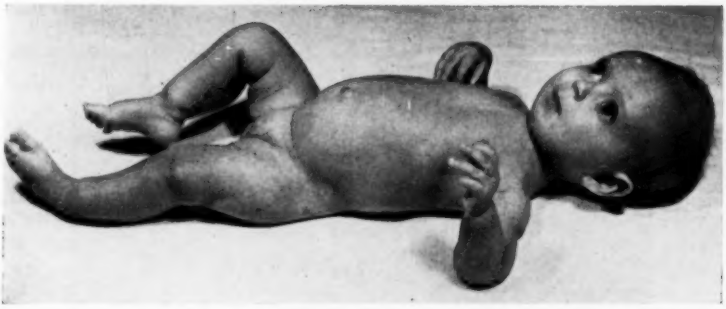
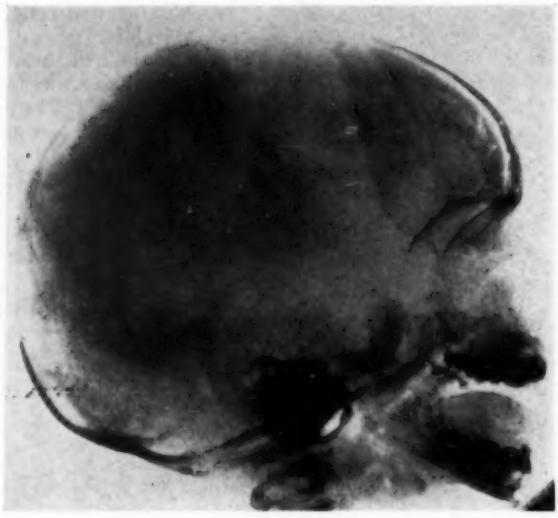


Fig. 1.—Photographs of the infant at the age of 6 months. Note the bulging fontanel.

On admission (May 4, 1953), when she was 6 months of age, she weighed 5,380 grams. Length was 62 cm. She was pale (Hb 9.6 Gm. per 100 ml.) and was much wasted but not clinically dehydrated. The infant seemed to be fairly lively; the mental development seemed to be normal. There was gross hypotonia. There were moderate rachitic rosary and swelling over ankles and wrists. There was no deformity of the chest or of the long bones. The circumference of the head was 41.5 cm. The anterior fontanel was bulging but not strikingly tense. The posterior fontanel was open, 3 × 4 cm. There was diastasis of 2 to 3 cm. between all bones in the calvarium. There were symptoms of a mild pharyngitis. The heart was of normal size; there were no murmurs. The systolic blood pressure was 205 to 220 mm. Hg. Examination of the eyes showed normal media and fundi; no signs of increased intraocular pressure. There was no other clinical abnormality. The child's appearance on admission is shown in Fig. 1.

*We are indebted to Dr. I. Alm for sending us the patient.



*A.*

*B.*

Fig. 2.—*A*, X-ray picture of the skull. Large diastases between the different bones in the calvarium due to absence of mineralization. Unerupted teeth seem to be normal. *B*, X-ray picture of the right side of the thorax and of the right shoulder region and humerus. Note the general low degree of mineralization, especially in the metaphyses of the humerus. Healing fractures in some of the ribs.

*Progress.*—The child was hospitalized until her death at the age of 10 months (Aug. 27, 1953). The condition was rather stationary during the first two months of her stay; during the last two months she became progressively more ill. The weight gain completely ceased (weight July 5, 5,300 grams; August 25, 5,250 grams). There were repeated upper respiratory tract infections with fever. Also marked anorexia; during the last month of life the baby was fed by tube. There was slight constipation and vomiting of moderate intensity. She was retarded physically; mentally she was normal. The muscle hypotonia remained unchanged. The systolic blood pressure was always increased (160 to 240 mm. Hg). The child showed a growth of only 3 cm. during the last four months. The extremities became rather short in relation to the length of the trunk. At the age of 9 months a sharp thoracolumbar kyphosis appeared. The circumference of the head remained relatively unchanged. There was possibly an increasing softness in the calvarial bones. The skeletal changes were otherwise as on admission. There were increasing respiratory difficulties with deep retractions owing to softness of the thoracic skeleton. The child died with symptoms of pulmonary and cardiac failure (pulmonary atelectasis, emphysema and hypertension).

*Investigations.*—There was a constant but slight normochromic anemia. The Wassermann reaction was negative. The urine (specific gravity 1.004 to 1.016) was, in general, acid (pH 5.0 to 6.5). A trace of albumin was almost constantly present. There were no pus cells. There was no microscopic hematuria, no casts; no abnormal excretion of amino acids or of ketone bodies. The excretion of calcium was somewhat higher than normal (93.6 mg. in three days) with a serum-calcium concentration of 12.0 mg. per 100 ml. The electrocardiogram was normal.

*X-ray Examination.*—There was no radiological evidence of renal calcification. Kidneys were of normal size. Renal pelvis was normal, calices not deformed. Urethrocystogram was normal. Repeated urographies showed varying but always reduced concentrating ability. The skeleton showed low mineralization generally. At all metaphyses there were considerable fraying, fragmentation, and deformation. Distinct changes were also in the structure of the epiphyses. There was a normal number of bone centers. Fig. 2 shows x-ray pictures of the skull and of the right half of the thorax with the right humerus.

The *blood chemistry* is given in detail in Table I. There was a constant but mild hypercalcemia. The level of serum phosphate was, on the whole, normal. The alkaline phosphatase activity in blood serum was lower than normal. Besides these changes there was a slight but constant increase of the nonprotein nitrogen. The acid-base balance was normal with the exception of the terminal period; there was normal serum concentration of sodium and potassium. There was a considerable increase of the $\alpha_2$-globulin. Such increase of $\alpha_2$-globulin was observed in idiopathic hypercalcemia[6] and is a usual finding in different renal lesions. There was no hyperlipemia (serum cholesterol 200 mg. per 100 ml.).

The infant reacted in a normal way to the subcutaneous injection of 50 units of parathyroid hormone (Parathyroid Extract, Lilly, was used). The serum calcium level rose from 13.1 to 15.6 mg. per 100 ml. in the course of twenty-four hours.

In order to exclude a phosphatase inhibitor in the serum of the patient her serum was mixed with serum from another case with high serum phosphatase activity (D-refractory rickets). From Table II it appears that there is no evidence for the occurrence of any substance that might inhibit the phosphatase activity.

*Post-mortem Examination.*—Examination revealed a malnourished under-

developed girl, 65 cm. in length. The bones of the skull were soft and thin. The fontanels were very wide and bulging. There was normal development of the bones of the face, and a small thorax. A marked projection of the costochondral junction, especially toward the thoracic cavity was noticed and near the spine irregular thickening of the ribs, corresponding to old fractures. The long bones were distinctly shorter than normal with thin diaphyses, and the epiphyseal ends were slightly enlarged. Skeleton of the hands and feet were normal.

The heart weighed 45 grams. There was right dilatation, but the heart was otherwise normal. The spleen appeared normal on gross inspection and weighed 8 grams. The kidneys had a total weight of 54 grams; they showed a pronounced fetal lobulation and the outer surface was irregularly granular. The parenchyma was firm and pale and showed several white spots, as well as streaks running down to the papillae. The cortex was possibly somewhat reduced. The urinary tract was otherwise normal. Hypophysis, thyroid, parathyroids, adrenals, ovaries, pancreas, and thymus were normal to macroscopic examination.

TABLE I. BLOOD CHEMISTRY

| DATE 1953 | SERUM CALCIUM (MG. PER 100 ML.) | SERUM PHOSPHATE (MG. PER 100 ML.) | ALKALINE PHOSPHATE ACTIVITY (UNITS) | CARBON DIOXIDE COMBINING POWER (MEQ. PER 100 ML.) | SERUM CHLORIDES (MEQ. PER 100 ML.) | TOTAL BASES (MEQ. PER 100 ML.) | NON-PROTEIN NITROGEN (MG. PER 100 ML.) | TOTAL PROTEIN (GM. PER 100 ML.) |
|---|---|---|---|---|---|---|---|---|
| 3/10 | 11.0 | 4.8 | 3.3 | | | | | |
| 4/ 2 | | | | 23 | 101 | 152 | 55 | 6.3 |
| 5/ 8 | 14.0 | 7.0 | 4.0 | 23 | 100 | | 39 | |
| 5/26 | 9.5 | 7.2 | | | | 149 | 46 | |
| 6/ 2 | 12.2 | | 4.0 | | | | 56 | 5.8 |
| 6/25 | 12.9 | 7.3 | 4.0 | | | | | |
| 8/10 | | | | 13 | | | 59 | 6.0 |
| 8/20 | | | 4.0 | | | | 53 | |
| 8/24 | 12.0 | 6.6 | | | | | | |

Electrophoretic pattern of plasma proteins (5/16) showed increase of $\alpha_2$-globulin (15.6 per cent against average normal value 5.8 per cent) at expense of albumin (53.5 per cent). The pattern was otherwise normal. Total serum protein according to the method of Kjeldahl was 7.69 grams per 100 ml. There was normal serum concentration of sodium and potassium. pH in blood was 7.4.

TABLE II. ALKALINE SERUM PHOSPHATASE ACTIVITY

| EXPERIMENTAL CONDITION | TESTED IMMEDIATELY (UNITS) | TESTED AFTER 3 DAYS' STORAGE (UNITS) |
|---|---|---|
| Patient | 4 | 2 |
| Control case | 45 | 14 |
| Patient + + control case | 24 | 9 |

The same volume of serum from the patient and from the control case (vitamin-D refractory rickets) were mixed immediately following drawing of the blood samples. The samples were stored in a refrigerator.

*Microscopic Examination.*—The kidney showed pronounced interstitial fibrosis with focally occurring, rather abundant plasmolymphocellular infiltration. There were several shrunken and atrophic glomeruli with thickening, fibrosis, and hyalinization of Bowman's capsule; some glomeruli were completely hyalinized. There were no crescents in Bowman's capsule. The tubular apparatus was, in large areas, atrophic. The convoluted tubules were frequently widened and in several of them calcium casts were present. Deposition of calcium salts was also seen around the tubules and interstitially (Fig. 7, *B*). Arteries of different size were normal.

*The Skeleton.*—There was pronounced widening of the growth zone of the ribs, which was 2 to 5 mm. in

width. The proliferating cartilage was irregularly calcified, the boundary toward the bone tissue being very irregular. There was a reduced number of osteoblasts and osteoclasts. The formation of bone and the remodeling seemed to be reduced in intensity. Subperiostally there are rather abundant broad streaks of a moderately cell-rich, fibrous, in part hyalinized tissue, which had the appearance of atypical osteoid. The compact bone tissue in the diaphyses was of an immature type. In only a few areas could mature haversian systems be observed. The bone tissue had in the main the same appearance as that of a newborn baby. Considerable inhibition of the rebuilding processes was thus present, but a certain degree of osteoclastic destruction could be seen in some places.

*Endocrine Organs:* Hypophysis, thyroid, pancreas, adrenals and ovaries were normal. Four parathyroids were found. A number of the chief cells had a rather light-staining cytoplasm. No adenomas nor any marked hyperplasia was observed.

*Other Organs:* Liver, spleen and thymus were normal.

*Results of Special Examinations.—Examination of Bone Tissue:* Microradiographic examination of normal bone tissue has shown that it is not uniformly mineralized.[1] Thus in the compact bone different haversian systems have a varying density of calcium salts (Fig. 3, *A*). The lowest mineralization occurs in the young newly formed systems; as these become older the mineralization increases progressively. The highest degree of mineralization is found in old bone tissue which surrounds the haversian systems.

The microradiographic examination of the bone tissue from this case showed, as did also the histological examination, that its development did not correspond to the age of the subject. The diaphyses in the long bones had on the whole the same appearance in this child of 10 months of age as they normally have at birth, both as regards their structure and the degree of mineralization. Fig. 3, *A*, *B*, and *C*, shows the microradiograms from the diaphysis of the tibia in a 10-month-old child without skeletal disease, from a newborn baby, and from the patient. A divergent feature from what is observed in the newborn baby is, however, the absence of distinct cementing lines. In normal compact bone tissue from newborn infants one finds clear, very highly mineralized cementing lines running circularly round the long axis of the bone. In the corresponding areas from this case there was suggestion of a boundary between different parts of the bone tissue. This boundary, however, appeared microradiographically to be due to a lower mineral content than that in the surrounding tissue rather than an area of increased calcification. The bone tissue in this case consisted almost exclusively of primitive, rather uniform, and fairly highly mineralized bone, and haversian systems occurred in only a few areas. In certain regions resorption cavities could be observed. The number of resorption cavities varied considerably in different parts of the diaphyses; in general, they occurred sparsely. The scanty newly formed bone tissue also lacked the cementing lines which otherwise normally mark off old bone tissue from the newly formed. From Fig. 4, which is a higher magnification than the foregoing figure, it appears that the newly formed calcified areas are a good deal poorer in cells than normal bone tissue. In the microradiogram the osteocytes appear as oval or round, somewhat irregularly formed areas, translucent to x-rays.

Decalcified sections examined in transmitted light showed in certain areas characteristic haversian systems. In polarized light one observed here the circular arrangement of collagen bundles typical for normal osteones. The microradiogram of these parts show, however, that the systems have a low degree of mineraliza-

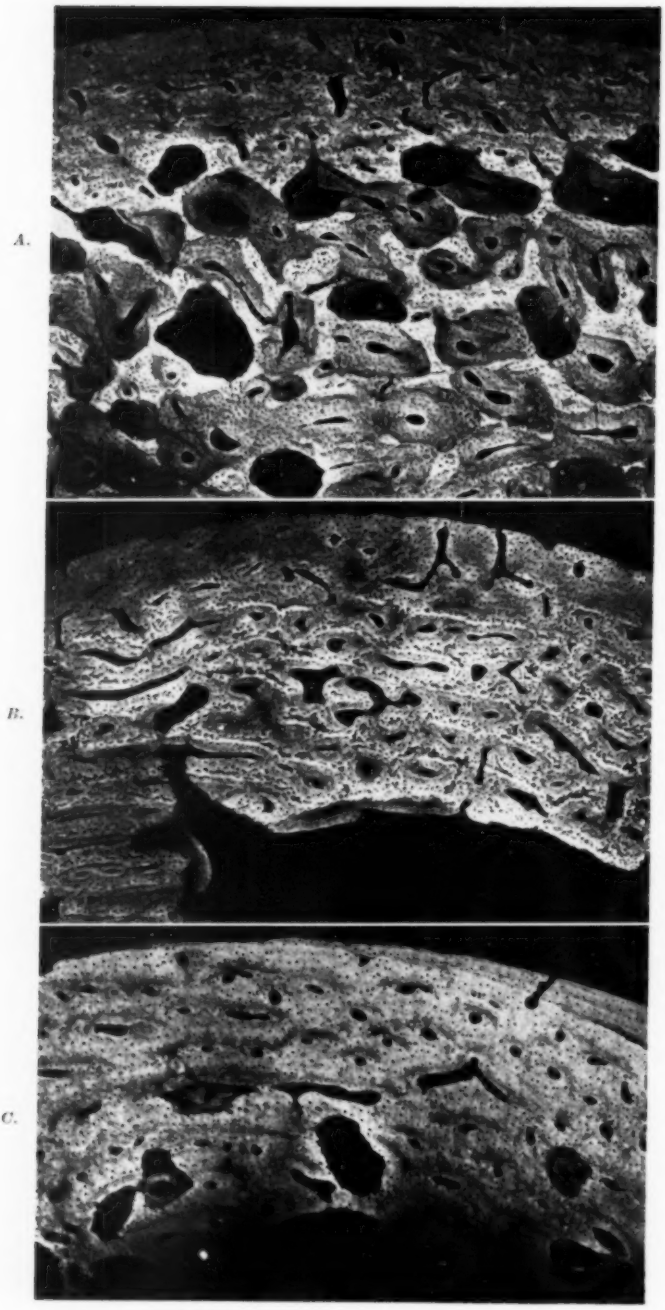


Fig. 3.—*(For legend, see opposite page.)*

tion and lack the normal gradient for calcium density.[1] Further some haversian systems were entirely without mineral salts (Fig. 5, *A*, *B*, and *C*.). Occasionally one finds systems in which only half the circumference is mineralized. These findings are never observed in normal bone tissue. Nor does one find in cases of severe rickets haversian systems with a complete collagen pattern but with a total absence of calcium salts. Apart from the few haversian systems the collagen of the bone tissue occurred in the form of short, irregularly arranged bundles. The difference between the organization of collagen in this bone and in normal bone of the same age may be seen on comparing Fig. 5, *B* and Fig. 6.

*The Ion Exchange in the Skeletal Tissue:* The uptake of $Ca^{45}$ in vitro was very slight and occurred mainly endosteally and periosteally, and in the few haversian systems; this finding indicated that the processes of rebuilding were considerably inhibited.[9]

*Examination of the Ultrastructure:* This has been performed with the use of x-ray diffraction. The mineral salts in this case showed the same crystallographic patterns as does normal bone. The structure was that of a hydroxyapatite, and the dimensions of the unit cell were: c-axis 6.88 Å, a-axis, 9.41 Å.

*Examination of the Kidney Tissue:* In order to obtain quantitative data concerning the amount of deposited calcium salts in the kidneys and to be

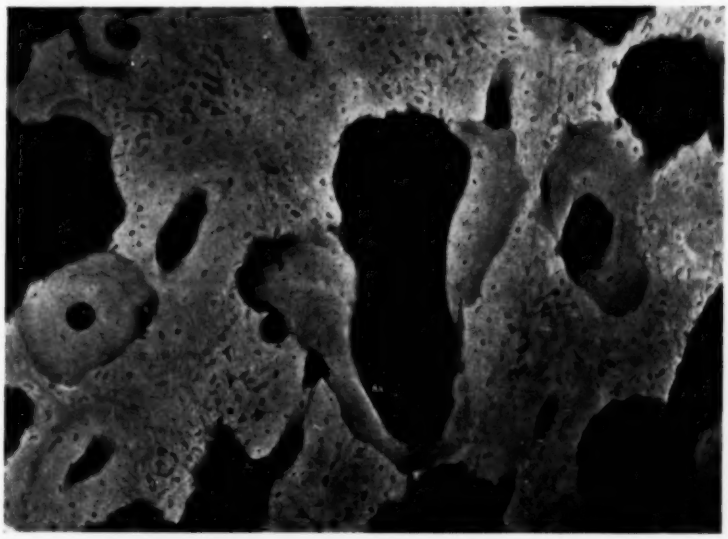


Fig. 4.—High magnification from an area of the same specimen as in Fig. 3, *C*. The microradiogram shows resorption cavities and the formation of haversian systems, which appear, however, to be abnormal in many respects. See text.

Fig. 3.—Microradiograms of transverse ground sections of femoral diaphyses. (×36; reduced 3/7.) *A*, From a 10-month-old infant with no signs of skeletal disease at death. At this age there is a relatively broad outer circumferential lamella. Most of the primitive bone is replaced by a bone tissue consisting of haversian systems of different degrees of mineralization. Owing to the high rebuilding intensity at this age, a fairly large number of resorption cavities are observed. *B*, From a new-born infant. The bone tissue consists of primitive lamellar bone. Note the broad, highly calcified cementing lines arranged circularly to the bone axis. In this period of development no distinct haversian systems exist. *C*, From the patient. The bone tissue is in the main of the same type as in the newborn infant, but poorer in cells. A few resorption cavities may be seen.

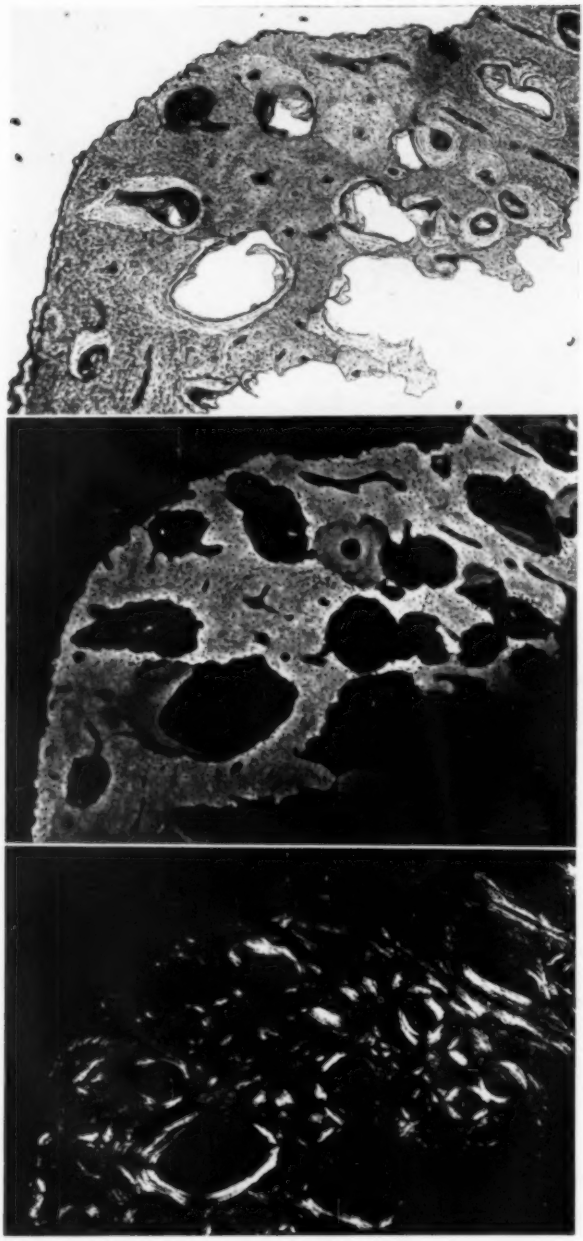


Fig. 5.—Transverse ground section of a specimen from the femoral diaphysis of the case described. (×30; reduced ⅔.) *A*, Decalcified section in transmitted light. *B*, Microradiogram of the same section before decalcification. *C*, The same section taken in polarized light after decalcification. The haversian systems formed have a normal collagen pattern. Some of the systems are calcified; others, however, are either completely uncalcified or mineralized only in a minor sector. The collagen pattern in the primitive bone is irregular, and the content of collagen is low.

able to judge the localization, the tissue was microradiographed. Fig. 7, *A* shows that the precipitation of calcium salts was most pronounced in the inner third part of the cortex, but that calcium salts also occurred abundantly in the collecting tubules of the medulla. The distribution of calcium-salt deposits in the kidneys resembled that observed in cases of vitamin D intoxication in the rabbit.[2]

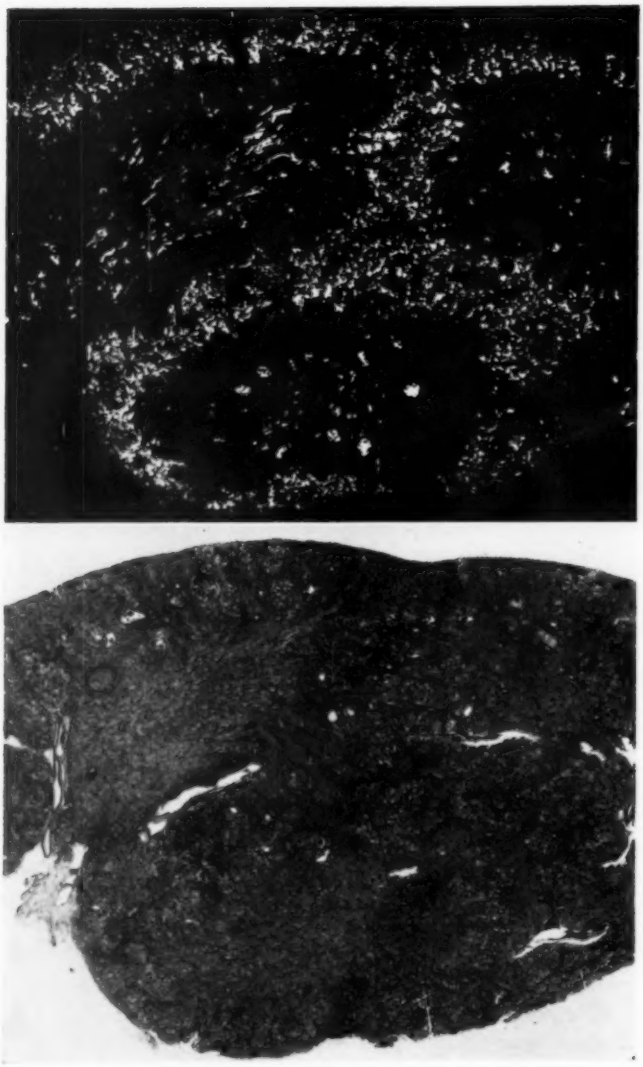
*Alkaline Phosphatase Activity in the Skeleton and Kidneys:* On account of the low alkaline phosphatase activity in the serum, the activity of this enzyme was determined in autopsy specimens from the skeleton and from the kidneys. Table III shows that this activity was low both in the bone tissue and in the kidneys. Whether the low activity in the kidneys was the result of the nephrocirrhotic changes or whether there was a primary enzyme deficiency cannot be established.

*Summary of the Clinical and Pathological Findings:* A generalized skeletal disease and a renal lesion was diagnosed in a girl at the age of 5 months. There were indications that the disease was of fetal origin. X-ray studies showed changes resembling those found in severe rickets. In the skeleton there was a retardation of growth which was most pronounced in the calvarial bones. Probably as a result of the renal lesion there was a consistent hypertension, slight hyperazotemia, and mild albuminuria. There were no symptoms of disturbed acid-base equilibrium. There was a moderate hypercalcemia, but the alkaline phosphatase activity in the blood serum was low. No signs of endocrine dysfunction were found. From the age of 6 months until she died at the age of 10 months she did not gain weight nor was there any increase in the length of the extremities. She died with symptoms of pulmonary and cardiac failure.

Fig. 6.—Decalcified transverse section of normal compact bone taken in polarized light (bone from the same case as in Fig. 3, *A*). Note the regular arrangement of collagen in lamellar bone and in the haversian systems.

Autopsy revealed that the bone tissue was abnormal in many respects. The compact bone was primitive and resembled that found in newborn infants. The remodeling processes which are normally started after birth were highly retarded and only a few haversian systems were formed. The abundant occurrence of atypical osteoid tissue indicated that the process of calcification was greatly disturbed. Furthermore the alkaline

*A.*



*B.*

Fig. 7.—*A*, Microradiogram of a section of the kidney (200 micra in thickness). The figure shows the distribution of calcium salts in the parenchyma. Most of the calcium salts were localized to the inner cortical layer. (×5; reduced ⅕.) *B*, Kidney section, 10 micra in thickness, cut from the specimen shown in *A*. Stained with hematoxylin-eosin. There were widespread areas of fibrosis and many of the tubules were dilated.

TABLE III. ALKALINE PHOSPHATASE ACTIVITY

(Buch and Buch units per kilogram of wet tissue)

| TISSUE | PATIENT | CASE WITHOUT SKELETAL DISEASE |
|---|---|---|
| Bone | | |
| Rib near costochondral junction | 210 | |
| Tibia, diaphysis | 120 | 500-2,500 |
| Tibia, growth zone | 170 | |
| Kidney | 250 | 800 |

For the experimental conditions see Methods. The control case was 13 months of age at death. The values for alkaline phosphatase varied between 500 and 2,500 in ten samples taken from different parts of the skeleton.

phosphatase activity was very low in the bone tissue and depressed in the kidneys.

## DISCUSSION

The most characteristic features of the skeletal disease described in this report are inhibited skeletal development, considerably reduced rebuilding of bone, and deficient mineralization of newly formed organic matrix.

The retarded growth of the extremities, the small diameter of the diaphysis, and the wide diastases between the bones of the calvarium are signs of general inhibition of bone development. The old bone in this case was highly mineralized. However, as the cortical layer of the long bones was thin the ordinary x-ray examination revealed a low absorption which might be wrongly interpreted as demineralization. Probably one reason why the bones of this case were fragile is that the collagen pattern was very like that of primitive bone.

The cause of the renal lesion cannot be fully established. It was present at the first examination, and at autopsy the kidneys showed characteristic changes of nephrocalcinosis. In infancy this type of renal disease often develops in connection with chronic acidosis.[18] Since in our case the blood chemistry did not reveal any signs of acidosis, the kidney calcifications must have another etiology. The consistent hypercalcemia can hardly be the result of bone destruction since the microradiographic investigation has shown that bone resorption was inhibited. Furthermore the persistent immature bone was highly calcified. However, the renal calcifications were certainly caused by the hypercalcemia. The abnormality was probably a consequence of the fact that there was an excess of calcium resorbed from the gastrointestinal tract in relation to that laid down in the skeleton. A renal lesion of the same type as in this case is found in chronic hyperparathyroidism,[15] a disease with hypercalcemia and a secondary renal lesion. The parathyroids, however, showed no abnormalities suggestive of primary parathyroid disease. Since the investigation did not reveal any evidences that the skeletal changes were secondary to a renal disease the skeletal abnormality may be considered to be primary. This conclusion is in harmony with the findings that the skeletal disease exhibited characteristics suggesting that it was of fetal origin.

These clinical and pathological studies revealed results resembling those obtained by Rathbun[22] in his investigation of a case which he termed "hypophosphatasia." In Rathbun's case, a male infant who died at the age of 9 weeks, there were metaphyseal changes resembling those found in severe rickets. In the entire skeleton there was markedly low mineralization and the calvarial bones were poorly developed.. In the blood

serum there was slight hypercalcemia and a raised nonprotein nitrogen level. The alkaline phosphatase activity was extremely low in the serum bone tissue, kidneys, and in the intestines. In the kidneys, hyaline casts were frequently formed in the collecting tubules and the tubules often gave the appearance of dilatation. Microscopically the bone architecture was consistent with rickets with abundant osteoid. Recently Sobel, and associates[24] described a case exhibiting some of the same clinical features as those reported by Rathbun.[22] In a 19-month-old girl severe rachitic changes and premature loss of deciduous teeth were observed. There was no growth defect and no signs of renal disease. There was a normal serum calcium level and low blood alkaline phosphatase activity. Liver and costochondral biopsies showed decreased tissue alkaline phosphatase activity. In the same communication preliminary and incomplete data from five additional similar cases are given. All five cases had roentgenological signs of severe rickets and low serum alkaline phosphatase activity. Some of these cases had symptoms of renal disease.

The clinical findings in our case are in many respects the same as in renal rickets. If the condition were one of a primary renal disease one would expect to find, apart from rachitic metaphyseal changes, demineralization of bone of the same type as in osteitis fibrosa.[14] The histological findings and the definitely low resorption intensity and high bone density in the immature bone is against such a diagnosis. There are also similarities to chondrodystrophia calcificans, especially to cases exhibiting signs of renal disease.[16] The similarity is particularly great as in our case pseudoepiphyses with calcifications of the same distribution as in "stippled epiphyses" were present. Syndromes entitled "idiopathic hypercalcemia of infants"[6, 19, 21] and "chronic hypercalcemia with osteosclerosis, hyperazotemia, dwarfism, and congenital malformation"[12] may probably be compatible with an inhibited growth and reduced rebuilding capacity in the skeleton though the mineralization process is intact.

In the present investigation it has not been possible to establish any definite etiology for the disease. The low alkaline phosphatase activity in the blood serum and in the bone tissue may either be a symptom derived alternatively of a generally disturbed cellular function, or the enzyme deficiency may be the primary cause of the disease. There are strong indications that the enzyme alkaline phosphatase in one way or another is concerned with bone formation. It is still unknown, however, whether the enzyme acts upon the mineralization process or if its action is coupled to the formation of the organic matrix. Thus it is difficult to conclude whether the low phosphatase activity is the primary cause of the disease or whether it is secondary to the inhibited skeletal development and reduced rebuilding intensity. The low alkaline phosphatase activity in the kidneys does not necessarily mean that there is a defective capacity for synthesis of this enzyme. Extensive fibrosis of the renal parenchyma may probably give rise to considerably reduced activity of several enzymes. However, the findings of Rathbun[22] and of Sobel and collaborators[24] that

the phosphatase activity is low also in the liver and in the intestine gives support to the hypothesis that the disease is caused by a generalized deficiency of alkaline phosphatase. Unfortunately the phosphatase activity of the liver and of the intestine was not examined in our case.

The skeletal disease of which an account has been given in this report may be considered to be genetically determined and to be caused by disturbed cellular function. It might thus be referred to the same group of skeletal diseases as osteogenesis imperfecta and osteopetrosis, two diseases which are likewise caused by a disturbance in the development of skeletal tissue. It seems reasonable to assume that the disease is of fetal origin. Because of the characteristics of this condition we suggest it be termed osteodysmetamorphosis fetalis.

SUMMARY

Renal and skeletal disease, clinically resembling severe rickets, was diagnosed in a 5-month-old girl. The girl was under observation until she died at the age of 10 months. In the blood serum there were hypercalcemia and low alkaline phosphatase activity. Along with the usual morphological methods the skeleton was also investigated using biophysical techniques.

In the skeleton there was a generalized inhibition of growth and considerably reduced intensity in the rebuilding processes. The mineralization of newly formed organic matrix was defective or completely absent. The compact bone showed most of the characteristics of that in newborn infants. In the kidneys, there was nephrocalcinosis with nephrocirrhosis. At autopsy the alkaline phosphatase activity was low both in the skeleton and in the kidneys.

The connection between this disease and other, previously described syndromes with the same clinical features is discussed. The disease appears to be a well-delimited clinical and pathological entity which may be genetically determined and caused by a disturbed cellular function.

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# PHEOCHROMOCYTOMA IN A FOUR-YEAR-OLD CHILD

## Renal Hemodynamic, Pharmacologic, and Radiographic Studies

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THE diagnosis of pheochromocytoma and the management of patients with hypertension on the basis of these tumors have been greatly facilitated in recent years. More specific diagnostic methods and safer pharmacologic tests for epinephrine-secreting tumors have increased the accuracy of the preoperative diagnosis and significantly decreased the hazard associated with the operative removal of the tumor. While pheochromocytomas are uncommon in younger age groups, they represent a curable type of hypertension and thus deserve careful consideration in the differential diagnosis of hypertension in childhood.

This paper reports the clinical course and management of a 4-year-old child with hypertension due to a functionally active pheochromocytoma. Studies undertaken for diagnosis and for estimation of renal function before and after successful surgical removal of the tumor are described. The differential diagnosis of this condition in childhood and a summary of the literature are included.

### CASE REPORT

*History.*—A 4-year-old white male child was first seen Oct. 28, 1952, with the chief complaints of headache, excessive thirst, enuresis, constipation, night sweats, and marked anxiety. His health was good until the age of 18 months, when in spite of an excellent appetite he failed to gain weight. Shortly thereafter he seemed to experience increasing thirst, and nocturnal enuresis recurred. Constipation appeared and became progressively severe. By the age of 2½ years he had developed excessive diurnal sweating and drenching night sweats and was consuming large volumes of fluid (200 to 300 c.c. per kilogram per day). At 3 years he was definitely small for his age and previous growth pattern. His personality was characteristically anxious and irritable; extreme emotional upsets followed minor frustrations. At 3½ years, the previous symptoms were accentuated and the patient began to complain of severe paroxysmal headaches. These lasted from thirty minutes to two hours and were followed invariably by extreme irritability. At 4 years of age, a physician noted, in addition to the above, a blood pressure of 170/120 and referred the patient for study.

*Physical Examination.*—Examination revealed a small, anxious, emotionally labile, chronically ill child. Weight was 14.5 kilograms, height 92 cm., temperature 99.8 (rectal), pulse 124, respirations 24, blood pressure 180/115. The hands were noted to be puffy and plethoric but of good color and not tender. The fundi showed a moderate degree of generalized vascular spasm but no evidence of hemorrhage, exudate, or papilledema. Examination of the heart revealed $A_2$ greater than $P_2$ with a Grade 1 apical systolic murmur. The point of maximal impulse was in the fourth interspace in the left nipple line. The abdomen was moderately protuberant. Liver

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and spleen were of normal size. No unusual abdominal masses were noted, though owing to lack of patient cooperation, an entirely satisfactory examination of the renal areas was not accomplished.

*Laboratory Studies.*—The red blood count was 4.27 million; hemoglobin was 13.8 Gm. per cent; white blood count was 7,000 with 69 per cent polymorphonuclears, 28 per cent lymphocytes, and 1 per cent monocytes. Urinalysis was entirely normal. A concentration test with fluids restricted for twelve hours produced no unusual discomfort to the patient and revealed a specific gravity of 1.024 and a pH of 5.5. Blood urea nitrogen and creatinine determinations were normal. An electrocardiogram revealed a sinus tachycardia and some evidence of left and right ventricular hypertrophy. An oral glucose tolerance test with the administration of 1.75 Gm. of dextrose per kilogram of body weight revealed: fasting blood sugar 108 mg. per cent; after one hour 209 mg. per cent; after two hours 130 mg. per cent; after three hours 68 mg. per cent. Serum sodium was 147 meq. per liter, serum potassium 4.6 meq. per liter, and serum chloride 103 meq. per liter. Total circulating eosinophils were 155 per cubic millimeter. In the hospital, the measured *ad lib.* intake and output on a twenty-four-hour basis revealed a fluid intake of 1,600 to 3,000 c.c. per twenty-four hours and a urine volume ranging from 1,000 to 1,500 c.c. per twenty-four hours. A plain film of the abdomen showed no abnormalities. Skull films were normal. The intravenous pyelogram revealed downward displacement of the right kidney with indentation of the superior pole. The opaque media was excreted in good concentration bilaterally, and the calyceal pattern did not suggest an intrinsic renal mass.

### SPECIAL STUDIES

*Radiographic Examination.*—In an effort to define the exact location and relation of the suspected suprarenal mass to the right kidney, the patient was given light barbiturate sedation, and 550 c.c. of air was introduced into the presacral space for the purpose of extraperitoneal pneumography.[1] The patient experienced no discomfort and no untoward effects. Radiographic examination of the abdomen revealed the kidneys to be well outlined. The left kidney appeared to be normal in size and position. The right kidney was displaced downward and the axis altered so that the upper pole was rotated anteriorly and laterally. This was produced by a well-defined rounded mass about 6 cm. in diameter in the anatomic location of the right adrenal gland. Air delineated this mass from the upper pole of the right kidney and defined its medial and lateral margins. The superior margin of this mass was not completely demarcated on the initial film. However, a film taken some four hours later revealed a change in the distribution of the retroperitoneal air, now defining the superior border of the suprarenal mass.

*Pharmacologic Study.*—The possibility that a pheochromocytoma was present seemed excellent. Accordingly, the response of the patient's continuously elevated blood pressure was tested with two epinephrine and norepinephrine blocking agents (hereafter referred to simply as "epinephrine-blocking agents"). All blood pressures were taken in the supine position, utilizing a standard mercury manometer and a 9 cm. cuff. Fig. 1 demonstrates the drop in blood pressure following 5.0 mg. of piperoxan administered according to the technique of Goldenberg.[2] The response noted is typical of that expected in hypertension due to an epinephrine- and/or norepinephrine-secreting tumor. Because of the transient duration of the hypotensive response and the difficulty of controlling the blood pressure continuously with piperoxan, additional observations were made using a newer epinephrine-blocking agent, Regitine, 2-(N′-p-tolyl-N′-m-hydroxyphenylamin-

omethyl) imidazoline. This drug will bring about a hypotensive effect, when given in appropriate dosage, whether administered orally, intravenously, or intramuscularly to patients with pheochromocytomas. Fig. 1 shows the response to 1.0 mg. of Regitine given intramuscularly and Fig. 2 a subsequent trial on 2.5 mg. intramuscularly. With either dose a significant drop in blood pressure was obtained; however, with the larger dose the drop in blood pressure was not greater but was more prolonged. This is in keeping with the data suggesting the specificity of the drug's peripheral epinephrine blockade at this dosage level and its lack of effect on other portions of the pressor mechanism. The sensitivity of our patient to graded oral doses of Regitine is shown in Fig. 3. The 12.5 mg. oral dose apparently produced incomplete epinephrine blockade. The 25 and 37.5 mg. oral doses established a complete epinephrine blockade. Side effects were absent. Although lack of patient cooperation made the detection of minor degrees of postural hypotension impossible, no episodes of acute postural hypotension were encountered.

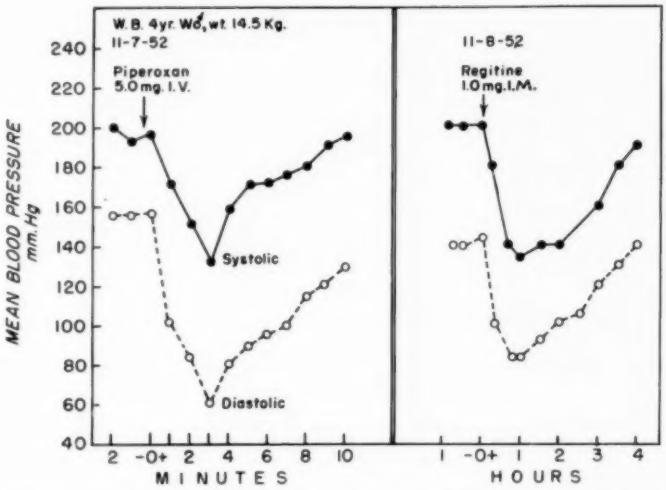


Fig. 1.—Response of blood pressure to piperoxan and Regitine in a patient with a proved pheochromocytoma.

*Renal Hemodynamics.*—The symptoms referable to the kidney, that is, polyuria and polydipsia, led us to suspect some degree of permanent renal functional impairment. This suspicion was increased by a feeling that the patient had probably been hypertensive since the onset of symptoms, two years before admission. Renal function studies were therefore carried out in the pre- and postoperative periods, with standard clearance techniques being used.[3] The glomerular filtration rate (GFR) was measured by the clearance of inulin, the renal plasma flow (RPF) by the clearance of para-aminohippurate, and the renal blood flow (RBF) was calculated from the Wintrobe hematocrit (duplicate). The filtration fraction (FF) was calculated as the ratio of glomerular filtration rate to renal plasma flow (GFR/RPF). The mean blood pressure (MBP) is the diastolic plus one-third of the pulse pressure. Renal vascular resistance is expressed as the ratio of the mean blood pressure to the renal blood flow (MBP/RBF). Table I enumerates these findings. In the preoperative, hypertensive state, the GFR and RPF

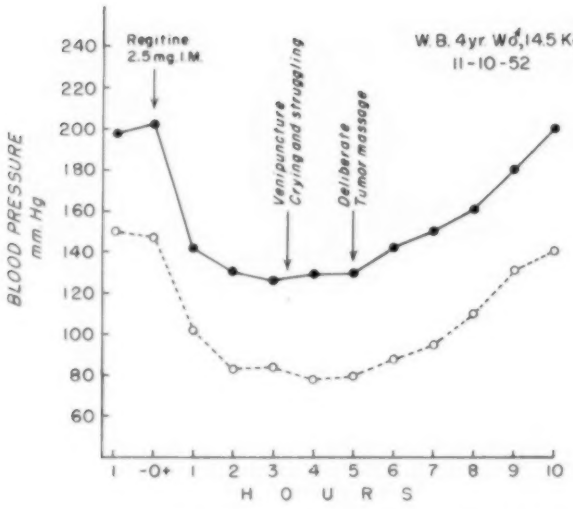


Fig. 2.—Response of blood pressure to Regitine in a patient with a proved pheochromocytoma.

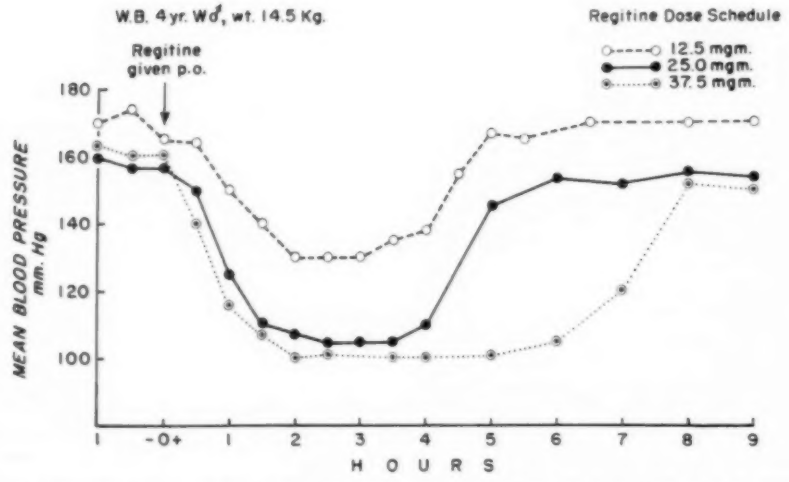


Fig. 3.—Hypotensive response to graded oral doses of Regitine in a patient with a proved pheochromocytoma.

are relatively normal in spite of the high value for renal vascular resistance. In the postoperative period there is a significant increase in the RPF and RBF without significant change in the GFR. This results in a reduction of the FF and is associated with a marked reduction in the renal vascular resistance value.

*Course in Hospital.*—Approximately ten days prior to surgical removal of the tumor, the patient was placed on oral Regitine, 25 mg. every four hours. During this period of continuous epinephrine blockade, the blood pressure remained consistently in the range of 120-140/70-80. The patient experienced no headaches or hyperhibrosis; the polyuria and polydipsia disappeared, and he seemed to be less nervous. No side effects of drug therapy were noted, and he pursued normal hospital activity during this period.

On the day of operation the last dose of oral Regitine was given, approximately two hours prior to surgery. Preoperative medication consisting of 200 mg. of phenobarbital per rectum and 0.32 mg. of atropine subcutaneously was given one hour prior to surgery. The blood pressure fell to 90/60 during the vinethene-$N_2O$ induction of endotracheal ether anesthesia, then rapidly returned to 110/80 as the abdomen was entered and the tumor was examined.

A transverse muscle-cutting incision was made in the right upper quadrant of the abdomen. This was enlarged into the ninth intercostal space, splitting the diaphragm. The left adrenal was normal to palpation. The right adrenal area was occupied by a firm rounded tumor. The vascular supply was divided with as little disturbance of the tumor as possible. The right renal vein overlay the lower anterior surface of the tumor. The inferior vena cava lay in an indentation on the anterior surface medially; here the main adrenal vein passed directly out of the tumor into the overlying vena cava, so that ligation was difficult. After the blood supply was divided, the tumor shelled out easily. An extraperitoneal drain to the tumor bed was brought out posteriorly. The wound was closed in anatomic layers with interrupted 0000 silk.

TABLE I. PRE- AND POSTOPERATIVE RENAL FUNCTION STUDIES CORRECTED TO 1.73 SQ. M SURFACE AREA

| | BP MM. HG | MBP MM. HG | GFR C.C./ MIN. | RPF C.C./ MIN. | RBF C.C./ MIN. | FF | F C.C./ MIN. | RVR | HCT |
|---|---|---|---|---|---|---|---|---|---|
| Average normal | 105/70 | 83 | 80-130 | 550-700 | 1,000-1,300 | 0.2 | 2-12 | 0.07 | 43 |
| Preoperative | 190/110 | 137 | 145 | 690 | 1,400 | 0.2 | 4 | 0.1 | 51 |
| Postoperative | 110/60 | 77 | 155 | 1,100 | 2,300 | 0.13 | 5 | 0.03 | 49 |

*Pathological Report.*—The gross specimen consisted of a large, firm, rounded mass of tissue which appeared well circumscribed. Attached to one border of this mass was a portion of thin, golden-yellow substance resembling adrenal cortex. The color of the tumor mass was light tan to pinkish-gray. Measurements were 7.5 by 6 by 6.5 cm. Weight was 122 grams. The tumor mass was examined by step sections. It cut with some resistance and with a slightly gritty sensation. The cut surface was moist and bulged slightly. It had a nodular, slightly lobulated character and a creamy tan color. A portion of the specimen is fixed in bichromate solution for special study.

Several microscopic sections were similar in their histologic appearance. Over the surface of one section was an adrenal gland with a definite thin surrounding capsule and with cortical cells retaining an intact architecture. The zona glomerulosa was indistinct, but the zona fasciicularis was clearly

defined with columns of polygonal small adrenal cells having very pale cytoplasms and small vesicular nuclei. At one point remnants of adrenal medullary cells were found. The tumor mass that was described in its gross appearance existed completely extraneously to the adrenal and in part encompassed the gland. At no point could any direct origin from the adrenal gland be demonstrated. Portions of the tumor which were fixed in Zenker formol were studied. Similar histologic changes were present in these sections as in those fixed by formalin. The tumor was comprised of fibrillary material existing in disorderly array with numerous plump cells possessing large nuclei and prominent nucleoli and resembling nerve ganglion cells. In many instances the intervening substance is faintly fibrillary or finely granular. Many of these cells have short stubby processes which resemble the processes of ganglion cells. Scattered through the section are other smaller cells with small central nuclei and deeply acidophilic cytoplasms. Occasionally in these cytoplasms the Zenker formol-fixed tissue has scattered fine brown granules.

Histologically, this tumor is a mixture of nerve ganglion cells and smaller cells which are consistent in their appearance with pheochromocytes.

*Pathologic Diagnosis.*—Pathologic diagnosis was retroperitoneal tissue, ganglio-neuro-pheochromocytoma.

During the operative procedure and the immediate postoperative period, the blood pressure remained relatively stable without the use of any additional epinephrine-blocking agent or the need for vasopressor drugs. Immediately postoperatively, as is frequently the case, the patient's blood pressure remained moderately elevated.[16] By the ninth postoperative day, however, the blood pressure had fallen to a stable value of 110/60. Oral Regitine (37.5 mg.) now produced no change in the patient's reclining blood pressure. The patient was discharged in good condition on the twelfth postoperative day. He has remained asymptomatic to the time of this writing, fifteen months later. During this period he has gained 5 kilograms in weight and has grown 11 cm. in height. None of the presenting symptomatology has recurred. Subsequent urinalysis, blood pressure readings, and electrocardiograms have been within normal limits.

## DISCUSSION

L'abbe[4] first described hypertensive crises in association with a suprarenal tumor in 1922. Four years later, in 1926, Roux[5] reported the first successful surgical removal of such a suprarenal tumor. Subsequent to these reports some 280 cases[6] have been described in the medical literature. Many of these were found unexpectedly at operation or at the time of necropsy. The great majority have been present in adults. No significant sex difference has been noted in either adults or children. Anderson[7] reviewed a series of 768 benign tumors of children seen over a fifteen-year period and found only 0.3 per cent were pheochromocytomas. We were able to review sixteen published reports[2, 8-20] of typical functioning pheochromocytoma in children less than 14 years of age. The findings presented by these children plus the findings in the patient reported here are summarized in Tables II, III, IV, and V. Because of the lower incidence of this disease in children, most of our knowledge of the clinical picture, diagnostic criteria, and management of these patients is gained from the study of adult patients. The clinical symptomatology of the adult patient, as described by Smithwick,[21] is similar to that of the child in all significant respects.

TABLE II. PRESENTING COMPLAINTS IN SEVENTEEN CHILDREN WITH PROVED PHEOCHROMOCYTOMA

| COMPLAINT | NUMBER |
|---|---|
| Headache | 7 |
| Hyperhidrosis | 7 |
| Weakness and weight loss | 6 |
| Pain | 4 |
| Nervousness and anxiety | 2 |
| Visual disturbance | 2 |
| Polyuria | 2 |

Pheochromocytoma may vary in size from 5 mm. to 28 cm. in diameter. They are usually benign, though Symington and Goodall accept seven of the reported cases in the literature as unquestioned examples of malignancy. Two malignant tumors have been reported in children.[10, 11] Pheochromocytoma may be found wherever sympathetic chromaffin tissue occurs. Approximately 90 per cent[21] of all chromaffin tumors originate in the adrenal medulla. About 20 per cent of the patients in whom the tumor is of adrenal medullary origin will be found to have multiple and bilateral tumors. Abdominal pheochromocytoma of extra-adrenal origin are described in about 10 per cent of the reported cases. Three instances of an intrathoracic pheochromocytoma have been recorded,[22, 23] and a single intracranial tumor is described by Cahill.[22]

The clinical symptomatology and course in the adult or child with a functionally active pheochromocytoma is essentially the picture of chronic adrenaline intoxication or of sympathetic hyperactivity and has been appropriately referred to as the adrenal-sympathetic syndrome. Holton[24] demonstrated that the pressor substance liberated by these tumors consists of two catechols, epinephrine and norepinephrine. In the quantitative assay of three tumors, he found increased amounts of each of these substances per gram of tumor tissue. It is important to note, however, that the size of the tumor and its epinephrine and/or norepinephrine content does not always correlate with the severity of the patient's clinical findings. In general, the norepinephrine content predominates and it is felt that this substance is primarily responsible for the episodes of paroxysmal hypertension. Experimental studies have demonstrated that epinephrine within physiologic and therapeutic ranges is an over-all vasodilator and increases blood pressure only by increasing cardiac output. Norepinephrine, conversely, is an over-all vasoconstrictor agent and has little effect on heart rate and cardiac output. Variations in the clinical picture may be explained in part on the type or combination of hormones produced, as well as the amount of hormone in the circulation at any one time.

TABLE III. SUMMARY OF THE HISTORY IN SEVENTEEN CHILDREN WITH PROVED PHEOCHROMOCYTOMA

| SYMPTOMS | NUMBER |
|---|---|
| Anxiety and nervousness | 16 |
| Hyperhidrosis | 16 |
| Headache | 13 |
| Pain | 9 |
| Polyuria and/or polydipsia | 8 |
| Polyphagia | 6 |
| Constipation | 2 |
| Age onset of signs and symptoms: 2-12 years | Average: 7 years |
| Age diagnosis: 4-14 years | Average: 10 years |
| Sex: 11 males and 6 females | |

Chromaffin tumors were classically depicted as producing attacks of paroxysmal hypertension; however, subsequent experience has shown that many of these patients go on to exhibit a persistent or "essential" type of hypertension. Kremer[8] believes that

the initial paroxysmal nature of the hypertension may be overlooked in many cases since the patient seeks medical advice only when the continuous symptomatic hypertension appears some months or years later. Many of the reported cases, as well as the case reported here, support this impression. In children paroxysmal hypertension seems to be the exception rather than the rule. In some patients with a sustained blood pressure elevation, however, episodes of extreme hypertension (systolic pressures above 300 mm. Hg) may be superimposed and may lead to a fatal outcome.

TABLE IV. SUMMARY OF THE PHYSICAL AND LABORATORY FINDINGS IN SEVENTEEN CHILDREN WITH PROVED PHEOCHROMOCYTOMA

| SIGNS | | | NUMBER |
|---|---|---|---|
| Hypertension: | Sustained | 15 | |
| | Paroxysmal | 2 | 17 |
| Retinopathy | | | 16 |
| Resting tachycardia | | | 15 |
| Peripheral vasomotor changes | | | 12 |
| Underweight | | | 11 |
| Intravenous pyelogram abnormal | | | 7 |
| Fasting blood glucose above 80 mg. per cent | | | 6 |
| BMR significantly elevated | | | 6 |

Peripheral vasomotor phenomena were found in 90 per cent of the cases seen by Smithwick[21] and in 47 per cent of the cases he reviewed from the literature. In each of the twelve juvenile patients in which this finding was specifically commented upon, some evidence of unusual peripheral vasomotor phenomena was described. These consisted of episodes of pale, clammy extremities with a bluish-red discoloration of the hands and feet. The changes noted probably represent the vasoconstrictor effect of norepinephrine on the cutaneous arterioles. Smithwick emphasizes that these findings are rare in essential hypertension and that their presence should lead one to suspect the presence of a pheochromocytoma.

TABLE V. TUMOR AND PROGNOSIS IN SEVENTEEN CHILDREN WITH PROVED PHEOCHROMOCYTOMA

| | | NUMBER |
|---|---|---|
| Tumor: Solitary | | 9 |
| Extra-adrenal | | 2 |
| Bilateral | | 8 |
| Operative exploration: | Number | 13 |
| | Died | 7 |
| Not operated: | Number | 4 |
| | Died | 4 |
| Total deaths | | 11 |

A tendency to episodes of profuse, generalized sweating has been frequently noted in patients with functionally active pheochromocytoma. This symptom occurred in 90 per cent of the juvenile cases reviewed here and in 90 per cent of the adults seen by Smithwick. In addition, he found this symptom described in 52 per cent of the cases he reviewed in the medical literature. Two possible explanations have been offered to explain this hyperhidrosis. One is that since the sweat glands are innervated by sympathetic cholinergic fibers, the excessive sweating is merely a compensatory mechanism for the dissipation of heat in the presence of excessive endogenous heat production. The elevated basal metabolism, weight loss and increased appetite, and frequently the presence of elevated basal body temperature tend to support the probability of excessive heat production. Experimentally another possibility has been introduced by the observation that sweat glands will respond to both adrenergic and cholinergic drugs,[25] thus suggesting the direct participation of adrenergic substances such as epinephrine in the mechanism of the hyperhidrosis.

Several interesting variations have been described in the medical literature. Goldenberg[2] describes an adult patient with marked hypertension who, during his crisis, experienced a spontaneous hemorrhagic necrosis of his right suprarenal tumor, with subsequent drop of his blood pressure to only slightly elevated levels. At the time of necropsy some weeks later, examination of the right suprarenal gland revealed that at least 90 per cent of the chromaffin tissue had been destroyed by the episode of hemorrhagic necrosis. A particularly unusual case not included in our summary chart is described by Neff and associates.[26] A white female infant was apparently normal up to 8 months of age, at which time she began to develop extensive hirsutism and acne. At the age of 16 months she showed obesity and marked generalized hirsutism. The labia were hypertrophied and adult in appearance. The systolic blood pressure ranged from 140 to 180 mm. Hg. Bone age and skeletal maturation were advanced. Since this picture is more commonly associated with Cushing's syndrome, the mass palpated in the region of the left adrenal was assumed to be an adrenal cortical tumor. However, following its removal, pathologic examination revealed a normal cortical zone surrounding a greatly hypertrophied adrenal medulla. The tumor was identified histologically as a pheochromocytoma, though the clinical picture presented was not at all similar to the typical pheochromocytomas described in either adults or children. The authors postulated that the clinical picture of Cushing's syndrome might be explained by pressure of the tumor on the cortex with subsequent functional abnormality of the latter. Operative removal resulted in a regression of the abnormal findings as well as the hypertension.

Studies of renal function by the clearance technique pre- and postoperatively in these patients are rare. Wilkins and associates[27] describe their findings in a 22-year-old man whose hypertension had probably existed for several years. Their reported values for glomerular filtration rate, renal plasma flow, and filtration fraction were within normal limits. Calculation of the relative renal vascular resistance from the data given shows a marked increase in the preoperative period and a fall to normal in the postoperative normotensive state. In the course of their study they observed a hypertensive crisis of unusually severe degree. During this crisis the patient's filtration fraction rose to unusually high values as the renal blood flow decreased by almost 50 per cent of normal. The glomerular filtration rate remained normal. This episode was associated with an extreme rise in the renal vascular resistance. These findings are similar to those of Moyer and Handley[28] in experimental studies of renal hemodynamics in dogs. They found a marked increase in renal vascular resistance following the administration of epinephrine and norepinephrine, an effect which could be prevented by the administration of blocking agents. In untreated cases the prognosis is invariably poor owing to the irreparable damage to the heart and kidney. Our patient and the patient described by Wilkins[27] suggest that this poor prognosis need not necessarily be applied to the treated patient. In both instances, the increase in relative renal vascular resistance is present

only in the untreated hypertensive state. This finding emphasizes the importance of early diagnosis and treatment in the patient with hypertension due to pheochromocytoma.

The use of epinephrine-blocking agents in the diagnosis and management of patients with hypertension due to pheochromocytoma was first reported by Goldenberg in 1947.[2] He demonstrated a characteristic and significant fall in the patient's blood pressure within two to three minutes after the intravenous administration of piperoxan. This effect lasts five to fifteen minutes and is thought to result from the abolition of epinephrine effect on the pressor mechanism. Piperoxan is structurally similar to the catechols of the adrenal medulla and may act to form a reversible combination with the normal epinephrine receptors, thus transiently blocking the pressor effect of the sympathomimetic amines. Subsequent critical study of the piperoxan test[29] has confirmed its clinical usefulness but has also emphasized certain false positive responses and undesirable side effects. Goldenberg[2] lists the latter in order of decreasing frequency as: flushing, palpitation, nervousness, cold clammy extremities, hyperpnea, headache, fright and dizziness. None of these is sufficiently serious to preclude its use in the diagnostic study of hypertensive patients.

In 1949 Grimson[13] reported the use of Regitine as a relatively specific and safe diagnostic tool for study of the patient with hypertension due to pheochromocytoma. A tendency to elevation of blood pressure following Regitine administration in patients with essential hypertension is unusual and of minor degree. Side effects are limited to moderate tachycardia and in rare instances weakness, dizziness, and flushing. In addition, he demonstrated that control of the patient's blood pressure for long periods could be easily accomplished by the oral administration of Regitine. This form of medical management leaves the patient symptom-free and allows time for optimum preoperative preparation of each patient. Iseri and associates[17] satisfactorily used oral Regitine for twenty-seven days in the preoperative preparation of an 8-year-old child, and we experienced a satisfactory control of hypertension and no complications during ten days of preoperative oral Regitine therapy.

The presenting picture in the patient with hypertension due to a functionally active pheochromocytoma may readily be confused with a number of other disease states, namely, hyperthyroidism, central autonomic dysfunction, hypothalamic tumor, acrodynia, and Cushing's syndrome. Less commonly, a problem in differential diagnosis will be encountered in the patient with chronic nephritis, chronic lead poisoning, Wilms' tumor, diabetes mellitus, anxiety neurosis, coarctation, intracranial hemorrhage, and the occasional case of essential hypertension beginning in childhood.

The routine use of a battery of epinephrine-blocking agents as a screening procedure in all hypertensive patients is often helpful in identifying the patient whose hypertension is due to pheochromocytoma. However, in isolated instances false positive responses are obtained to these drugs, so that they cannot be used as the only basis for differentiation. As noted in Table V, the basal energy metabolism

(BMR) of the patient with a functioning pheochromocytoma is frequently elevated, therefore this test cannot be used to rule out the presence of hyperthyroidism. However, the serum protein-bound iodine and the uptake of radioactive iodine are both within normal limits in the patient with a pheochromocytoma, thus forming valuable adjuncts to differential diagnosis. The presence of peripheral vasomotor phenomena, tachycardia, marked irritability, excessive sweating, and weight loss are sometimes convincingly similar to acrodynia.[30] In the latter patients the hands and feet are quite tender and painful, excessive urinary excretion of mercury is usually present, and the patient's symptomatology often responds to BAL administration. Riley and co-workers[31] have described a syndrome of central autonomic dysfunction with defective lacrimation characterized by paroxysmal hypertension, vasomotor phenomena, drooling, hyperhidrosis, and defective lacrimation. These findings are, with the exception of the drooling and defective lacrimation, indistinguishable from those of the patient with a functioning pheochromocytoma. Recently, Aronson and associates[32] reported a patient with this syndrome in whom a typical hypotensive response to piperoxan and Dibenamine was obtained. This patient was subjected to careful operative exploration, but no pheochromocytoma could be found. While this does not entirely rule out the presence of small functioning pheochromocytoma hidden within the adrenal or within other solid organs, it again emphasized the need for caution in the interpretation of any so-called "specific" tests. The presence in several reported cases of polyuria, polydypsia, hypertension, and elevated fasting blood sugar in association with a diabetic glucose tolerance curve may be quite suggestive of hypothalamic tumor, Cushing's syndrome, or the degenerative phase of diabetes mellitus. The anxious appearance and severe irritability presented by some of these children may raise the question of an anxiety neurosis or primary behavior problem.

## SUMMARY

The clinical course and management of a 4-year-old child with hypertension due to a functionally active pheochromocytoma is described. The tumor was localized by intravenous pyelography and presacral air insufflation. Renal function was studied by the clearance technique in the pre- and postoperative periods. The diagnostic response of our patient to both piperoxan and Regitine is described. Subsequent to successful operative removal of the tumor, the patient's abnormal signs and symptoms disappeared. Sixteen cases of hypertension due to pheochromocytoma collected from the literature are reviewed. The typical findings in children appear in every aspect similar to those found in adults with functionally active pheochromocytoma, as described by various authors.

We wish to express our appreciation to Dr. Vincent P. Collins for the radiographic studies and for assistance in preparation of the text, to Dr. Wilson G. Brown for pathologic studies, and to Dr. Murdina M. Desmond and Dr. Russell J. Blattner for helpful criticism in the preparation of the manuscript.

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# THE PULMONARY TUBERCULOMA IN CHILDHOOD: ITS MEDICAL AND SURGICAL MANAGEMENT

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RESECTIVE surgical treatment of well-defined and isolated tuberculous pulmonary lesions in adults has become a widely accepted and successful procedure. Yet the applicability of radical resection of peripheral parenchymal lesions in children has so far not been unequivocally decided.

The following types of parenchymal tuberculomas (the term used in the broad sense of a well-defined area of granulomatous tissue reaction due to the *Mycobacterium tuberculosis* of Koch) can be classified as more or less distinctive entities.

1. Primary peripheral tuberculoma of minute size with the tendency to heal with or without radiological residuals.
2. Extensive primary or postprimary pneumonic lesions which tend to heal with more or less extensive fibrocalcific nodular residuals.
3. Reinfection type of isolated tuberculomas, oftentimes called "coin lesions."
4. Cavitary lesions, an unusually rare occurrence in children, which may develop either as a reactivation of a primary tuberculoma or as a result of disintegration of a secondary tuberculoma.

If we consider the criteria which guide us in the therapeutic management of adolescent and adult tuberculosis, these above-mentioned childhood types of pulmonary lesions pose the question of whether or not resective surgery, following a proper course of chemotherapy, appears applicable. According to Alexander,[1] "The removal of the most extensively diseased tissues, including cavities and caseous lesions, is obviously advantageous; scattered, active or potentially active parenchymal or bronchial lesions remaining in uncollapsed parts of the lungs may, or may not, become inactive in the course of time."

Up to the present there are conspicuously few reports available on pulmonary resections in childhood tuberculosis. Out of 426 patients who had undergone resective surgery for pulmonary tuberculosis Overholt[2] mentions only one patient 3 years old and one 8 years old. No details as to the nature of these resected childhood lesions are given. Levitin and Zelman[3] published four total pneumonectomies for advanced and progressive tuberculosis in children from Sea View Hospital. In a more recent article covering 235 cases of thoracic surgery for tuberculosis, Hughes[4] has not had one patient under 20 years of age.

There is a basic difference between the residual lesion, after chemotherapy, in the lung parenchyma of the mature person and the peripheral tuberculous process in the lungs at early and mid-childhood. It is the collateral lymphadenitis which represents the main, if not the only, differ-

From Muirdale Sanatorium of Milwaukee County and Milwaukee Children's Hospital.
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ential feature in childhood and adult tuberculosis. We know that all the lymphatic organs undergo a progressive involutionary development in adolescence.

Miller and Wallgren[5] stress the fact that "the characteristic feature of primary tuberculosis of the lungs is the accompanying swelling of the lymphatic glands of the hilum. These swollen glands are never so prominent in other forms of tuberculosis."

According to Price[6] the "endogenous spread takes place from a primary focus *or gland* which may be either active or partially healed or apparently healed." He further stated that "because of glandular involvement at this age, the risk of massive blood stream infection is greater, the large tumor-form swelling seen frequently in infants are but rarely seen in later childhood. At school age, glandular enlargement and perihilar activity are frequently seen but are less marked; hematogenous spread from these is usually limited to one or two metastases."

This prominent role played by the participation of the central tracheobronchial lymph nodes in the primary and postprimary tuberculous process has to be taken into account in considering the therapeutic management of such patients.

In the following we have selected eleven typical cases from the Children's Service of Muirdale Sanatorium and Milwaukee Children's Hospital of the last twenty-eight years, a total of roughly 1,000 inpatients (an average of thirty-six new admissions per year), which illustrate the four classes of childhood lesions previously mentioned, with the idea of evaluating the applicability of radical pulmonary resection for these different types of diseases.

As to the first group, that is, the typical primary tubercle itself, it seems an obvious fact that this has so far never been found tempting to the thoracic surgeon. The reason for this reluctance could not possibly be its harmlessness, because we know that the initial seed, the so-called Ghon's focus, may be the starting point of the most vicious pulmonary and extrapulmonary complications. The contraindication against the surgical approach rests with the simultaneous involvement of the regional lymph nodes, which does not permit anything like a complete removal of all the important foci except by total pneumonectomy.

Levitin and Zelman[3] in their article on pneumonectomy stress the same point: "A factor which may materially alter the prognosis in children, and which is only infrequently encountered in adults, is the lymph node component. This is present in both the primary and the adult types of pulmonary tuberculosis in children."

In considering the bipolar (or multipolar) nature of the primary complex in children, we are reminded of the analogy with a primary bronchogenic carcinoma that has invaded the collateral lymphatics and thereby progressed beyond the stage of operability.

Much the same considerations seem to be in order in questioning the validity of resective surgery in the second and third categories (which include the postprimary pneumonic lesions with their more extensive nodular residuals and the isolated secondary tuberculomas or coin lesions). In both cases there is the same factor of the

central foci in the tracheobronchial glands which is invariably present and would limit, thereby, any surgical procedure to a subtotal resection.

Houghton's[7] interpretation of these secondary circular lesions as inspissated cavities that may possibly act as a "time bomb" is, according to our observations in middle and later childhood, unjustified. While Shields and co-workers[8] found the reactivation rate of multiple nodular disease and of inspissated cavities in adults high and that of residual nodules from tuberculous pneumonia low, Mitchell[9] stated in a recently published survey of untreated tuberculomas in adults that "severe or fatal progressions of such lesions have been rare."

It is only in the rather exceptional instances of proved cavitary lesions that pulmonary resection should be considered alongside other more conservative and reversible methods of treatment. The danger of a bronchogenic dissemination or the improbability of cavity closure under nonresective therapy are strong arguments. The complete therapeutic success of excisional surgery in Case 11 helps to justify this method of treatment in destructive pulmonary tuberculosis in children. However, the one instance of Case 9, which shows complete disappearance of a giant cavity under artificial pneumothorax treatment and permanent healing after twenty-three years of continuous observation, points toward the validity of the more conservative approach, even in the rare instances of cavitary lesions in children.

## DISCUSSION

The cases of Andrew A. and Patricia D., both with distinct primary tubercles, impress us with the potential viciousness of any initial lesion, no matter how minute and no matter how distinctly calcified according to radiological standards. Andrew A. developed meningitis in spite of calcified Ghon's tubercle and hilar nodes. Patricia D. developed the following hematogenous metastases: tuberculous peritonitis, bilateral tuberculous nephritis, cervical tuberculous lymphadenitis, tuberculous arthritis.

There is no doubt that it is not the harmlessness of the primary tubercle which constitutes a contraindication against radical excision but only the bifocal nature of the primary complex as seen invariably in these as in all other cases of primary tuberculosis.

The postprimary type of extensive unilobar or multilobar tuberculous pneumonitis is represented by the cases Joseph T., Jesse N., and Patricia J. All three showed excellent response to chemotherapy (in one instance to what we would now consider entirely insufficient chemotherapy) and progressive fibrocalcific involution and healing for periods of from five to seven years of close observation. The three cases of Patricia E., Joan A., and Dianne K. are quite comparable, as they represent the emergence of a secondary isolated tuberculoma which occurs not infrequently in later childhood. All three resulted in complete, or almost complete, radiographic clearing under chemotherapy.

In the case of Thomas C. (Case 10) an apparently solid nodular lesion either turned out to be an inspissated cavity or gradually disintegrated into a small central excavation as one of the so-called "time bombs." This grew into a giant cavity which again

decreased in size under antibiotic therapy. At this point there was a choice between artificial pneumothorax and resective surgery. The latter resulted in one of the very few fatalities on our service. In contrast to this stands the record of the comparable case of Doris S. (Case 9) who, also with a giant cavity, long before the advent of antibacterial and excisional therapy, obtained prompt cavity closure and permanent healing following conventional collapse therapy by pneumothorax. Our last case, that of Larry A., presents the rare clinical picture of extensive necrosis and liquefaction in the right lung of a 3-year-old Negro child. Extensive resections, preceded and followed by combined chemotherapy, apparently resulted in complete healing without any vestige of radiological residuals.

Fig. 1.—Case 1. Calcified primary complex followed by tuberculous meningitis.

Our conclusion is that the proper identification and classification of isolated nodular lesions in children's lungs will lead to a proper therapeutic program which, as a rule, will be entirely successful without radical surgery.

CASE REPORTS

CASE 1.—Andrew A., a 16-month-old infant, was admitted to the hospital on July 22, 1950, with tuberculous meningitis, with a partially calcified primary tubercle, and also a calcified, very large hilar lymph node. Spinal fluid was positive. Streptomycin 0.5 Gm. and PAS 1.5 Gm. were given daily from July 22, 1950, till Jan. 23, 1951. The patient was discharged on May 24, 1951, completely recovered and without any neurological residuals. On the last follow-up examination, Jan. 28, 1954, he was completely well.

CASE 2.—Patricia D., a 26-month-old infant, was admitted to the hospital on Dec. 20, 1943. There was a small left hilar lesion, no visible peripheral tubercle, tuberculous serous peritonitis, and, a few months later, bilateral tuberculous nephritis. Gastric and urine cultures were positive for tuberculosis. Also, there was a cold abscess of the cervical gland, as well as tuberculous arthritis with destructive epiphysitis of the left knee. The primary and metastatic processes showed a progressively favorable healing tendency without chemotherapy. The chest film of Sept. 26, 1946, showed a completely calcified primary complex. On Sept. 23, 1949, streptomycin therapy was started prior to fusion operation on the left knee, on Jan. 12, 1949. On March 22, 1950, the patient was discharged, with the primary tuberculosis, tuberculous peritonitis, renal tuberculosis, and tuberculous arthritis of left knee apparently healed.

CASE 3.—Jesse N., 2 years 8 months of age, was admitted to the hospital on June 9, 1949, with extensive left tuberculous pneumonitis. Cultures were positive. For four months he was given streptomycin. Then, after a four-month period of intermission, he was given streptomycin and PAS for three months. The patient was

discharged on April 28, 1951, with the tuberculosis inactive. There have been periodic re-examinations at from three- to six-month intervals, during which three gastric cultures have been taken. The patient remained healed when last examined, on Jan. 18, 1954.

bronchitis with stenosis. Streptomycin 0.3 Gm. daily (without PAS) was administered from June 10 till Sept. 24, 1949. The first gastric culture was positive; all others were negative. The patient was discharged on Dec. 29, 1950. He remained completely

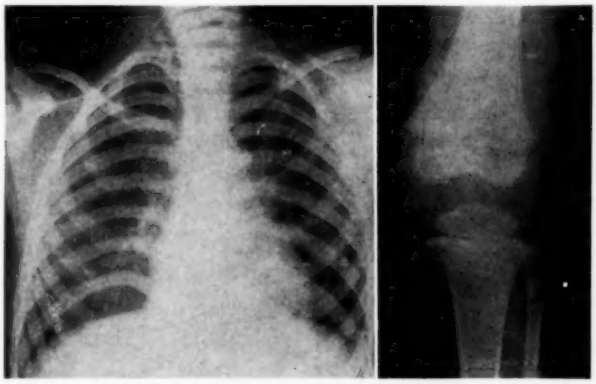

Fig. 2.—Case 2. Primary complex followed by tuberculous peritonitis, tuberculous nephritis, tuberculous lymphadenitis, and tuberculous arthritis of knee

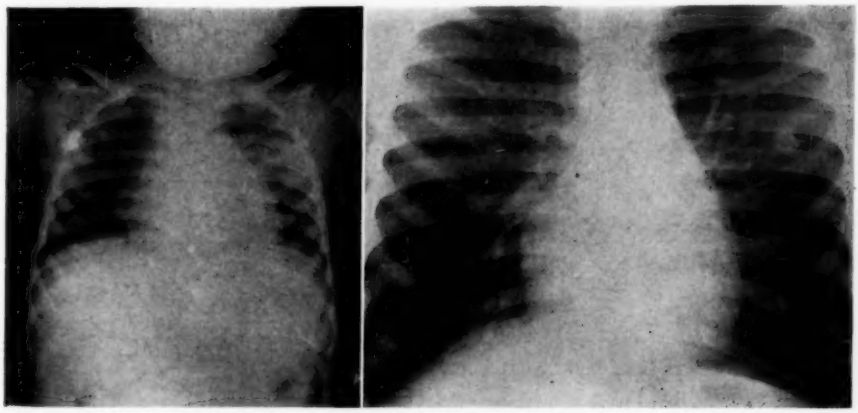

Fig. 3.—Case 3. Tuberculous pneumonitis with residual tuberculoma; patient apparently healed for three to four years.

CASE 4.—Joseph T., 3 years 3 months of age, was admitted to the hospital on April 18, 1949, with tuberculous pneumonitis of the entire right upper lobe, as well as tuberculous

healed, with large calcareous residual, numerous negative cultures at the last x-ray examination, Feb. 5, 1954.

CASE 5.—Patricia J., 3 years 9 months of age, was admitted to the

hospital on Aug. 19, 1947, with tuberculous pneumonitis with hilar adenopathy, guinea pig inoculation positive. Streptomycin 0.5 Gm. was given for only ten days. The patient was discharged on Sept. 7, 1947. Close follow-up examinations were given at

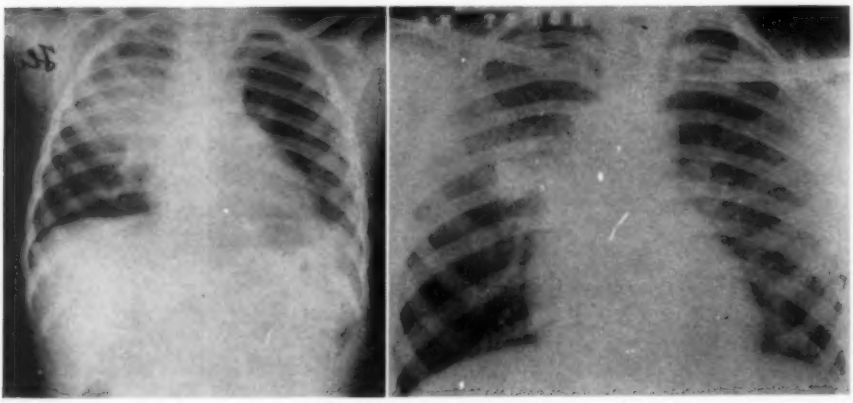

Fig. 4.—Case 4. Tuberculous pneumonitis with residual large central calcification; patient remained healed for three to four years.

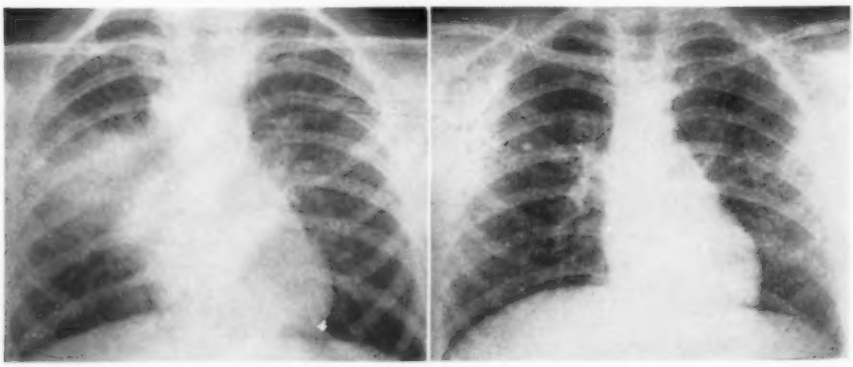

Fig. 5.—Case 5. Tuberculous pneumonitis with calcified nodular residual; patient remained healed for six to seven years.

from three- to six-month intervals. The patient remained completely healed at the last examination, Feb. 2, 1954.

CASE 6.—Patricia E., 9 years 4 months of age, was admitted to the hospital on May 25, 1951, having had a primary hilar lesion since 1948 (proved family exposure). In May, 1951, she developed a nodular lesion in the right mid-lung field. Streptomycin and PAS were administered daily from May 30, 1951, till Aug. 8, 1951, then twice a week till discharge on Sept. 2, 1951. Thoracotomy with resection was recommended on Oct. 16, 1951, but was declined by the parents. Previous therapy was continued until March 20, 1952. There was al-

most complete disappearance of the coin lesion, and the patient remained completely healed when observed in February, 1954.

CASE 7.—Joan A., 11 years 9 months of age, was admitted to the hospital on Feb. 5, 1952, with left minimal pulmonary tuberculosis and a coin lesion given daily from Feb. 11, 1952, till discharge on Oct. 1, 1952, then twice a week until Dec. 3, 1952. The patient's parents refused resective surgery. The last re-examination, on Feb. 10, 1954, showed the patient apparently healed, and gastric cultures were negative.

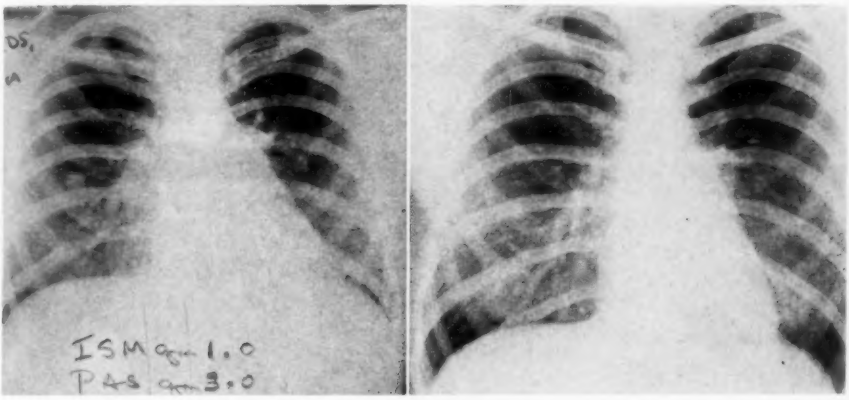


Fig. 6.—Case 6. Secondary tuberculoma with small calcified residual; patient apparently healed for two years.

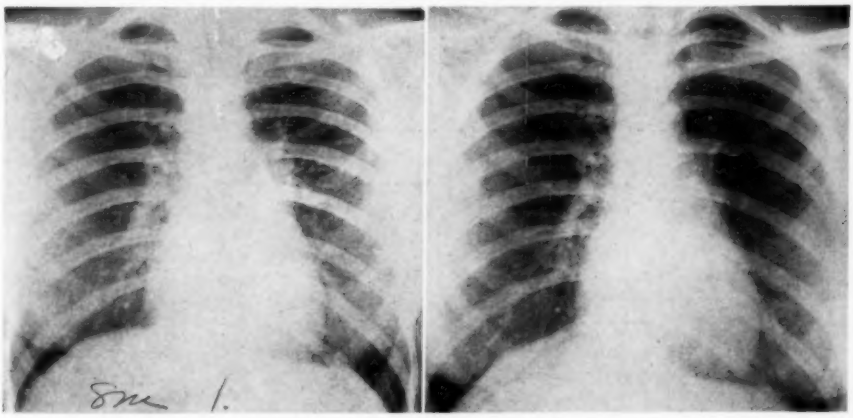

Fig. 7.—Case 7. Secondary subapical tuberculoma; patient apparently healed for two years.

of the left subapical region. Bacterial culture was negative. The father had active tuberculosis. Dihydrostreptomycin 1.0 Gm. and PAS 1.0 Gm. were

CASE 8.—Dianne K., 14 years 1 month of age, was admitted to the hospital on Feb. 16, 1953, with a left subapical tuberculoma (reinfection

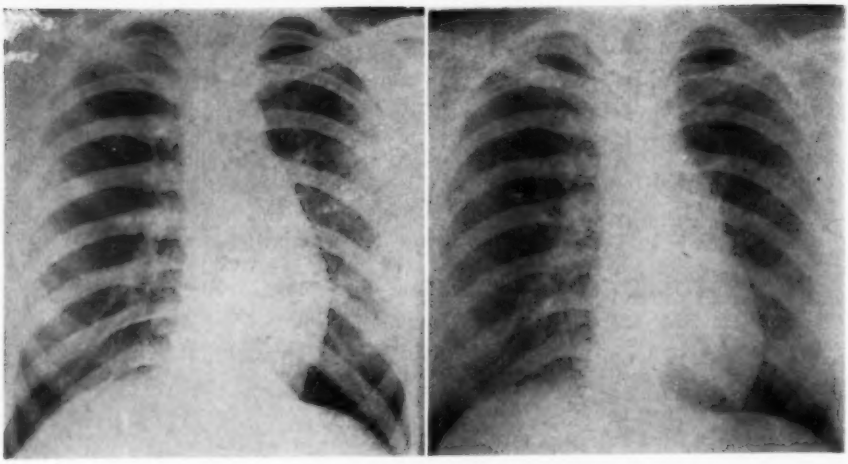

Fig. 8.—Case 8. Secondary lesion of left upper lobe; patient apparently healing, with minimal subapical coin lesion.

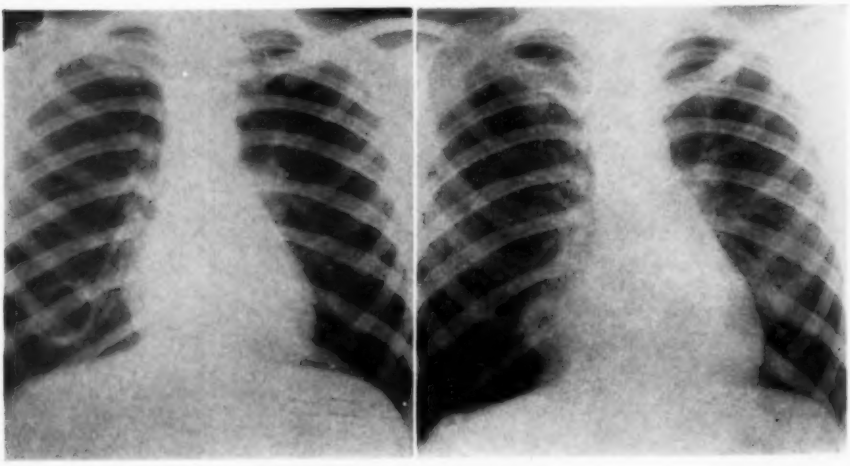

Fig. 9.—Case 9. Giant cavity secondary to calcified Ghon tubercle; pneumothorax therapy permanent healing for twenty-two years.

type). The gastric culture was positive. Therapy consisted of streptomycin and INH for six weeks, added PAS for three months; it was changed to intermittent streptomycin and PAS on Sept. 29, 1953. Left pulmonary resection was offered but was declined by the parents. The patient was discharged on Oct. 1, 1953, on ambulatory treatment previously given. There was clearing of the coin lesion and bacteriological conversion.

right lower lobe. Sputum was persistently positive. Pneumothorax treatment was started on Nov. 18, 1931, and was continued until April 26, 1933. The patient left the sanitorium against advice on April 29, 1933. She remained under continuous periodic observation, with the last x-ray examination on Jan. 19, 1954. There was no reactivation at any time. The patient remained completely healed

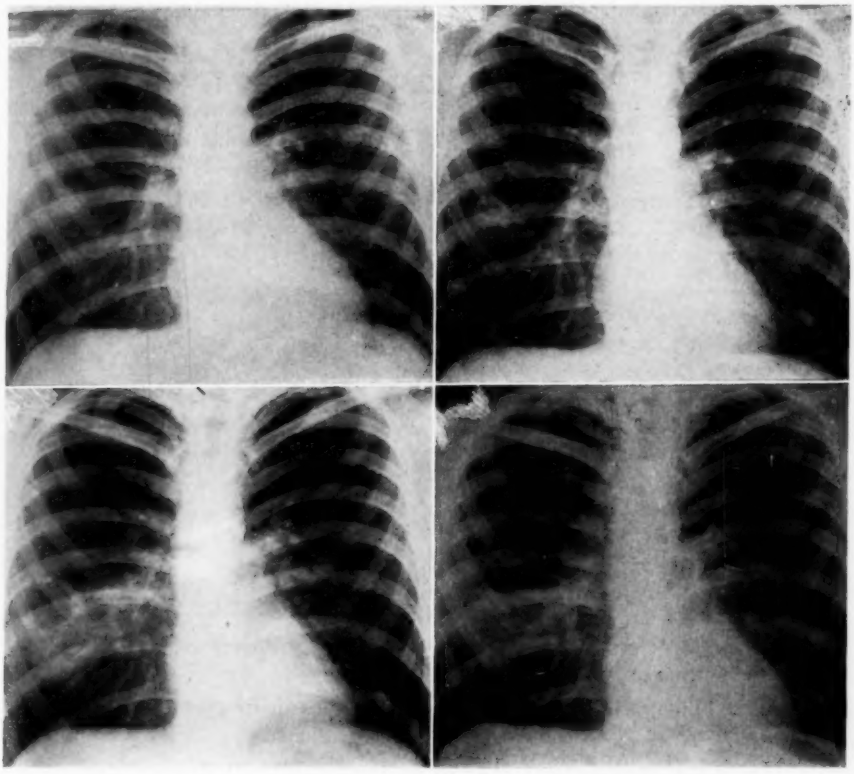

Fig. 10.—Case 10. Isolated tuberculoma of right mid-lung, followed by excavation, followed by giant cavity formation, followed by reduction through chemotherapy; unsuccessful resection.

Case 9.—Doris S., 10 years 3 months of age, was admitted to the hospital on Oct. 31, 1931, with moderately advanced pulmonary tuberculosis and with a large cavity due to reactivation of calcified primary tubercle in the twenty years after pneumothorax treatment.

Case 10.—Thomas C., 13 years 2 months of age, was admitted to the hospital on May 19, 1948, with right

minimal tuberculosis; a small, solid, circular lesion was present in the right mid-lung field. Three sets of gastric cultures and one bronchial specimen were negative. The patient was discharged on Oct. 14, 1948. He was readmitted on Aug. 4, 1949, with a small cavity in place of the tuberculoma. Cultures were positive. Streptomycin 1.0 Gm. was given daily, starting Oct. 14, 1949. The size of the cavity increased. Streptomycin was discontinued on Jan. 11, 1950, owing to partial resistance. The condition became worse; there was a cough and fever. Streptomycin and PAS were resumed on Feb. 17, 1950. The condition improved. There was a choice between artificial pneumothorax and resective surgery. On April 6, 1950, a lobectomy of the right lower and middle lobe was performed. The patient died owing to operative shock.

28, 1952, resection of the anterior segment of the right upper lobe was performed as well as wedge resection of the inferior division of the right lower lobe. Dihydrostreptomycin 0.5 Gm. and PAS 3 Gm. were continued till discharge on May 1, 1953. The patient remained healed with negative gastric cultures on last examination, Feb. 16, 1954.

## SUMMARY

1. A classification of tuberculomas in the pulmonary parenchyma of children is given: (a) the primary tuberculoma of minute size, (b) the more or less extensive nodular residual following postprimary tuberculous pneumonitis, (c) the reinfection type of isolated tuberculomas, (d) cavitary lesions following reactivation of primary or disintegration of secondary tuberculomas.

2. The prominent role played by the participation of the collateral lymphatic glands in children is demonstrated in eleven representative radiograms, and the impracticality of limited resective surgery is emphasized.

3. The progressive involution and radiological disappearance of second-

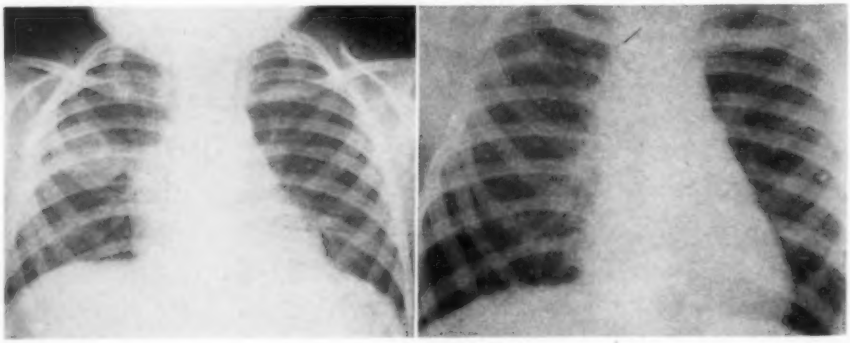

Fig. 11.—Case 11. Tuberculous pneumonitis with excavation and liquefaction; successful extensive resection.

Case 11.—Larry A., a 26-month-old infant, was admitted to the hospital on June 7, 1951, with far-advanced tuberculosis of the right lung and extensive consolidation and excavation in the mid-lung region. Aspiration of thick purulent material showed it positive for tuberculosis. Streptomycin 0.5 Gm. and PAS were administered daily from July 9, 1951, till July 2, 1952, twice a week till Oct. 2, 1952, then daily till Dec. 31, 1952. On Oct.

ary tuberculomas (coin lesions) under proper chemotherapy is illustrated.

4. The treatment of the rare instances of cavitary lesions in children by resective surgery and by pneumothorax is discussed.

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# ACUTE FERROUS SULFATE POISONING

## Report of a Nonfatal Case

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A CASE of acute ferrous sulfate poisoning is presented. A review of the literature reveals that most patients who received an equivalent amount did not survive. Many patients who ingested much less than this patient died. A brief review of the literature is included.

### CASE REPORT

S. B. (Henry Ford Hospital No. 720432), a 26-month-old white female infant, was admitted to The Henry Ford Hospital on June 25, 1953, at 2:30 P.M. Approximately two and one-half hours prior to admission the patient had ingested sixty-five proprietary iron capsules containing a total of 13 Gm. of ferrous sulfate. Of the original one hundred capsules in the bottle, twenty-five were found on the floor. Ten had previously been used by the mother. The composition of this preparation was ferrous sulfate, 0.2 Gm., and molybdenum oxide, 3.25 mg.

The patient had been left alone, temporarily, and when found, shortly after ingestion, was very lethargic and retching violently. Her legs were soiled with a large amount of black feces.

The past history was negative except for tonsillitis at 6 months of age.

Physical examination revealed a well-developed, well-nourished, lethargic white female infant, who responded minimally to external stimuli. The temperature was 99.4° F. rectally, the pulse was 150, and respirations were 26 per minute. The blood pressure was 90 systolic and 60 diastolic.

The child appeared acutely ill with shallow respirations, thready pulse, marked pallor, and weakness. The head, eyes, ears, nose, and throat were normal. The chest was clear to percussion and auscultation. The heart rate was rapid with sinus arrhythmia, but otherwise normal. Abdominal examination was not remarkable. Neurological examination revealed hypoactive deep tendon reflexes plus lethargy.

Immediately upon admission the child was placed in an oxygen tent, a Levin tube was passed, and normal saline was started intravenously. The stomach was lavaged with 500 c.c. of normal saline, bringing back greenish material with occasional flecks of bright red blood. No fragments of the capsules were recovered.

Following the lavage, 1 ounce of mineral oil and 8 ounces of 50 per cent milk-50 per cent cream mixture were left in the stomach. Ten ounces of a saturated solution of sodium bicarbonate were then started through the tube by slow drip.

The following treatment, modified after Spencer's,[21] was then instituted. A saline intravenous drip containing vitamin B complex was continued for approximately forty-eight hours. One hundred cubic centimeters of blood plasma was given intravenously the afternoon of admission.

The Levin tube was left in place and through this 4 ounces of milk-cream mixture and 0.2 Gm. of bismuth carbonate were given every four hours. Methionine, 500 mg., and Eprolin, 100 mg., were given every twelve hours through the tube.

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In addition, 30 mg. of dimercaprol (BAL) was given intramuscularly every four hours for forty-eight hours and every twelve hours on the third day.

This regimen was continued until the afternoon of the third hospital day when the Levin tube was removed and the medications were discontinued. Prophylactically, aqueous procaine penicillin, 300,000 units, and streptomycin, 100 mg., were given every six hours for the hospital stay.

The child improved rapidly, and within six hours she was fairly active but was still having many large tarry stools. There was no retching or vomiting after admission. Blood pressure and vital signs became and remained stable, and eighteen hours after admission she was removed from oxygen. She had no further difficulty except for a short period of lethargy and a mild drop in blood pressure approximately thirty-six hours after admission. The tarry diarrhea cleared forty-eight hours after admission, and she began to pass normal stools.

On the third hospital day she was given a soft diet and supplemental vitamins. The urine was tested three times a day from the third to sixth day for sugar and acetone because of the report on the second day, and only once did it give a one-plus Benedict's reaction. She tolerated the soft diet well, became completely asymptomatic, and was discharged on the sixth day.

Laboratory results were as follows:

First Day (four hours after ingestion): Hemoglobin was 13.7 Gm.; red blood cells 4,800,000; white blood cells 30,800 with 86 per cent neutrophils, 13 per cent lymphocytes, and 1 per cent monocytes. Carbon dioxide combining power was 22.6 meq. per liter; chloride 108 meq. per liter; serum iron 4.0 mg. per cent (normal in this laboratory, 0.1 mg. per cent).

Second Day: Hemoglobin was 12.4 Gm.; red blood cells 3,900,000; white blood cells 10,600 with 61 per cent neutrophils, 4 per cent eosinophils, and 35 per cent lymphocytes. Urine: specific gravity 1.027, alkaline, negative albumin, one-plus Benedict, positive acetone and diacetic acid; spun sediment; 4 to 6 leukocytes per field and numerous epithelial cells. Serum iron was 2.0 mg. per cent.

Third Day: Serum iron was 0.92 mg. per cent.

Fourth Day: Hemoglobin was 13.9 Gm.; red blood cells 4,800,000; white blood cells 7,200 with 44 per cent neutrophils, 2 per cent eosinophils, and 54 per cent lymphocytes. Stool: normal color and consistency, three-plus phthalein test for occult blood. Serum iron was 0.38 mg. per cent.

Fifth Day: Serum iron was 0.40 mg. per cent. Fasting blood sugar was 92 mg. per cent.

Sixth Day: Hemoglobin was 13.3 Gm.; red blood cells 4,500,000; white blood cells 8,150 with 27 per cent neutrophils, 1 per cent eosinophils, and 72 per cent lymphocytes. Serum iron was 0.87 mg. per cent.

A telephone conversation was had with the mother one month from the day of admission. She reported the child to be in excellent health.

## DISCUSSION AND REVIEW OF THE LITERATURE

Although many cases of oral iron poisoning were reported in the last half of the nineteenth century,[8, 11] the earliest case reported in the modern literature was that by Thomson.[23] This occurred in May, 1944, and was reported in 1947. Since then thirty cases, summarized in Table I, have been noted, with a fatality rate of 53.3 per cent.

Most modern textbooks of pediatrics still refer only to mild gastrointestinal symptoms as toxic effects of oral iron.[6] Forbes[10] and Spencer[21] quote earlier authors in reporting encephalopathy apparently due to oral iron therapy.

Most of the cases reported in the British literature involved ingestion

of a proprietary compound composed of 0.2 Gm. of ferrous sulfate, 2.5 mg. of copper sulfate, and 2.5 mg. of manganese sulfate. Forbes,[10] by animal feeding experiments, found the ferrous salt to be the toxic agent. Ferrous sulfate undoubtedly was the noxious substance in our case. Not much in-

TABLE I

| AUTHOR | CASE NO. | AGE (MO.) | SEX | DOSE (GM.) | TREATMENT | RESULT |
|---|---|---|---|---|---|---|
| Branch[1] | 1 | 29 | M | 18.0-22.5 | Lavage, $O_2$, heat, suction, IV fluid, blood | Died, 4½ hr. |
| Duffy and Diehl[2] | 2 | 15 | F | 4.9-6.4 | IV saline | Recovered |
| | 3 | 18 | M | 4.9 | Lavage, IV fluid, plasma, blood, penicillin | Recovered |
| | 4 | 26 | F | 9.75-13.0 | Lavage, heat, $O_2$, IV fluid, caffeine | Died, 4½ hr. |
| Forbes[10] | 5 | 39 | M | 10.0* | None | Died, 53 hr. |
| | 6 | 12 | M | 6.0-7.0* | Heat, milk, Nepenthe, $O_2$, atropine, penicillin | Died, 30 hr. |
| Foucar[11] | 7 | 26 yr. | M | 113.5 | Lavage, $O_2$, blood, artificial respiration | Died, 3 hr. |
| Lancet[8] | 8 | 16 | F | 8.0* | ? | Died |
| Lindquist[12] | 9 | 24 | F | 5.34† | Blood, penicillin | Recovered |
| | 10 | ? | ? | 10.68† | ? | Died |
| Murphy[13] | 11 | 30 | F | 15.0 | Lavage, Na bicarbonate, AlOH gel, penicillin, milk | Recovered |
| Prain[14] | 12 | 11 | F | ?* | Lavage, Na bicarbonate, sulfa, bismuth carbonate | Died, 39 hr. |
| Roxburgh[15] | 13 | 16 | M | 6.0-9.75 | Lavage, $MgSO_4$, IV fluid, penicillin, BAL | Recovered |
| Shoss[16] | 14 | 14 | F | 16.3-24.4 | Lavage, IV fluid, milk, $O_2$, penicillin, BAL | Recovered |
| Smith, J.[17] | 15 | 21 | M | 8.2* | Lavage, Na bicarbonate | Died, 4 hr. |
| Smith, R.[18] | 16 | 17 | F | 6.5? | Coramine, $O_2$, plasma, methylene blue, IV fluid | Died, 11 hr. |
| Spencer[21] | 17 | 21 | F | 10.8* | Lavage, Na bicarbonate, bismuth carbonate (serum iron: 4 hr., 3.3 mg.; 3 days, 0.26 mg.) | Recovered |
| | 18 | 23 | M | 5.8* | Saline, bismuth carbonate, vitamins,‡ IV fluid (serum iron: 4½ hr., 3.42 mg.; 6 days, 0.33 mg.) | Recovered |
| | 19 | 11 | M | 1.4-1.8* | Lavage, bismuth carbonate, vitamins‡ | Recovered |
| | 20 | 20 | M | 0.6* | None | Recovered |
| | 21 | 12 | M | ?* | Saline, castor oil | Died, 4 hr. |
| | 22 | 19 | F | 3.0-3.2* | Saline | Died, 4 hr. |
| | 23 | 18 | M | 8.8* | Lavage, stimulants | Died, 5½ hr. |
| | 24 | 14 | F | 8.0* | Castor oil, kaolin | Died, 20 hr. |
| Swift[22] | 25 | 19 | F | ? | IV fluid, blood, BAL, Penicillin, streptomycin, $O_2$, vitamin K, Amphojel | Died, 40 hr. |
| Thomson[23] | 26 | 16 | F | 5.2* | Lavage, Na bicarbonate, Nepenthe, bismuth carbonate | Died, 21 hr. |
| | 27 | 24 | M | 1.6* | Magnesium hydroxide, bismuth mist., IV fluid, milk | Recovered |
| Thomson[24] | 28 | 54 | F | 0.8* | Bismuth carbonate | Recovered |
| | 29 | 19 | M | 2.0* | Syrup of figs, lavage, Na bicarbonate, BAL | Recovered |
| | 30 | 30 | M | 2.0-4.0* | Syrup of figs, lavage, magnesium sulfate | Recovered |

*Also 12.5 mg. copper sulfate and 12.5 mg. manganese sulfate per gram of ferrous sulfate.
†Ferric chloride.
‡See text.

formation is available as to the toxicity of molybdenum, but Fairhall[9] states: "No toxic effects in workers exposed to the dust and fumes of molybdenum and its common compounds have been reported."

Notable in this case was recovery after such a large dose. Only two patients with a larger amount survived. Murphy and associates,[13] state that their patient never appeared acutely ill. Shoss[16] treated his patient in a manner similiar to ours.

Treatment was modified after Spencer,[21] as recommended in the JOURNAL.[7] He advocated immediate production of vomiting, followed by gastric lavage, leaving sodium bicarbonate in the stomach. He also suggested bismuth carbonate, 0.2 Gm., every four hours, and the following vitamin mixture: 10 mg. of aneurin hydrochloride, 30 mg. of nicotinamide, 10 mg. of riboflavin, 15 mg. of tocopherol, and 500 mg. methionine. (This to be multiplied by the age in years and divided into three doses per day.) Somers[19] first suggested the use of sodium carbonate or bicarbonate in order to produce insoluble ferrous carbonate and later[20] advocated the use of aluminum hydroxide and bismuth sulfate.

Dimercaprol (BAL) was used despite the controversy over its toxicity. Edge and Somers[3] report, after animal experiments, that the iron-BAL complex is more toxic than iron alone. However, the *British Medical Journal*[4] advocated its use "particularly where the metal has a characteristic sulfide." Thomson,[24] Roxburgh,[15] and Swift[22] used dimercaprol in their cases but did not evaluate it, whereas Shoss[16] thought it was a deciding factor in survival.

Murphy and associates[13] and Roxburgh[15] both reported positive urine sugar in their patients. It is our feeling that the two positive Benedict's reactions were due to nonspecific reducing substances and did not indicate hepatic, pancreatic, or renal damage with resultant abnormal carbohydrate metabolism or excretion as they were transient, and, in our patient, the blood sugar level was normal.

Spencer[21] reported serum iron determinations in two nonfatal cases (Table I, Cases 17 and 18) with results similiar to those recorded for this patient. Swift and associates[22] in their fatal case found a normal iron content in the liver and kidney. Smith[17] suggested that the intestinal barrier to iron is broken down by the initial large dose and raised the question that ferritin, acting as a vasodepressor substance, may cause the initial characteristic shock. He also suggested the possible value of using a phosphate salt for inhibition of iron absorption.

The *British Medical Journal*[5] states that, in all cases autopsied, there was a marked corrosive action on the gastric mucosa and less on the duodenum and small intestine. Prain[14] found definite necrosis and fatty metamorphosis in the liver and suggested that the absorbed iron was the toxic agent. Other authors and the JOURNAL[6] suggested that these changes are secondary to the shock resulting from the destruction of gastric mucosa.

Spencer[21] emphasized the characteristic picture of shock in four to six hours, improvement from twelve to thirty-six hours, and a second critical period from twenty to fifty-three hours. He also listed the classical

symptoms of pallor, coldness, tachycardia, retching, vomiting, drowsiness, and restlessness. He noted too that hematemesis was frequent, diarrhea uncommon, and the respiratory rate often rapid with shallow excursions.

This paper serves to re-emphasize the toxicity of ferrous salts and the necessity for rapid and conclusive treatment.

SUMMARY

1. A case of acute ferrous sulfate poisoning in a child with recovery is described.

2. A brief review of the literature is presented.

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# PHENOLPHTHALEIN IN CHILDHOOD

## Dosage and Efficacy

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White or yellow phenolphthalein, or a combination of these two forms of phenolphthalein, is employed as active ingredients in a large number of preparations for laxative effect. One hundred two preparations containing this substance, alone or in combination with other drugs, were listed in 1937 by Belote and Whitney.[1]

The fact that a large number of preparations contain phenolphthalein, and the satisfactory results obtained from it, may account for its extensive use as a laxative.

A survey of prescription ingredients was made by Gathercoal[2] in 1932. He found that in prescriptions filled at pharmacies ninety-seven out of 10,000 contained phenolphthalein, in comparison with only eight in the year 1907.

The wide use of phenolphthalein is probably due to several factors. It is tasteless and odorless and can be easily incorporated in a variety of vehicles. When taken at bedtime, it is not likely to disturb sleep and rest, usually producing an evacuation the following morning. It does not produce dehydration with a suitable dose. Beckman,[3] in his *Treatment in General Practice,* and Osborne and Fishbein,[4] in the *Handbook of Therapy,* consider phenolphthalein an excellent laxative. According to Beckman, "It produces a stool very much like the normal," and he states that "infants of eighteen months may be given as much as ½ grain (0.03 Gm.)."

The good opinion of phenolphthalein as a laxative, held by the majority of physicians, is not shared by some. Unfavorable opinions are mostly based on the questionable reports that appeared at various times, particularly in the early European literature during the first decade following the introduction of phenolphthalein into medicine.[5] A critical review of these reports reveals the purposeful devices employed to discredit the usefulness of phenolphthalein. Exaggeration of alleged untoward effects, omission of consideration of possible coincidence of manifestations, nonrecognition of allergic phenomena, the pyramiding of reports by some authors who, besides reporting their own observations, include the reports of others, possibly without realization that each of the others referred to the same group, have all tended to create an erroneous impression. Statements appeared which implied that phenolphthalein influenced unfavorably almost every organ in the body.

Against this background of unfounded reports of untoward effects attributed to phenolphthalein, originating mostly in Europe, careful investigations by several university

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groups* in this country resulted in a better understanding of the pharmacologic and therapeutic properties of this substance. These investigations also led toward dispelling the belief of supposedly noxious influences of phenolphthalein on various organs of the body. Moreover, they delineated the indications, contraindications, dosage, and the possible side effects in sensitized persons.

Since nearly all of the investigations in recent years were made on adults, the present study was designed to establish experimentally the optimum dose of white and yellow phenolphthalein for children and to determine comparatively the laxative activity of white and yellow phenolphthalein, the incidence of abdominal discomfort that may attend their use, the occurrence of reactions due to idiosynerasy, and the effect on blood cytology and hemoglobin and on the composition of the urine, as well as any effect this form of medication may possibly exert on the growth and development of children.

## TEST SUBJECTS

A group of fifty-six children was selected for this study, which extended over thirty-three weeks. By a preliminary four-week period of case-finding survey, the test subjects were classified as constipated (A) or non-constipated (B). The constipated group was comprised of those children who, prior to the beginning of the period of observation, repeatedly came to the attention of the physicians or nurses at the infirmary because of discomfort associated with infrequent, irregular, or difficult evacuations and in whom the discomfort was relieved when more frequent and regular bowel movements occurred, with or without the use of a laxative. Both groups were further divided into subgroups, those less than 6 years of age (A-1; B-1) and those over 6 years of age (A-2; B-2). Of the fifty-six children, constipation was present in one-half of the group.

## PROCEDURE

During a preliminary period of three weeks, daily records of the number and character of stools of each person were recorded. In this way, base figures were established for the average number of stools for each child per day, without the administration of a laxative. Medication was given to all children on the same day, usually at bedtime, and the number of stools for each twenty-four hours was recorded. The aggregate daily average was considered a "child day."

To assure absolute accuracy of dosage of the medication, the phenolphthaleins used were weighed individually on an analytical balance scale and, with approximately 15 grains of lactose added, the medication was placed on a powder paper. The two substances were lightly mixed on the paper, but were not triturated.

White phenolphthalein was given to one group and yellow phenolphthalein to another group so that the effect of these two forms of the laxative could be better compared and evaluated. A single dose was given rather than small, "broken" doses, because it was found by Fantus and Dyniewicz[6] that with phenolphthalein, fractional dosage resulted in a diminution or ab-

*Studies were made by groups at Cornell University, Temple University, and University of Illinois College of Medicine.

sence of cathartic action in some instances.

To determine the optimal dose and the most suitable interval for administering the laxative, in the first phase of the study Group A (constipated) was given white phenolphthalein in amounts of 1 to 3 grains, with intervals of two to five days between doses, for a period of eight weeks. Group B (nonconstipated) received yellow phenolphthalein under similar conditions.

The dose of 3 grains was decided upon as the maximum in this study because satisfactory increases in the number of stools were obtained in each child, without the occurrence of diarrhea after repeated administrations of this dose.

Following a rest period of one week, during which no medication was administered, yellow phenolphthalein was given to Group A and white phenolphthalein to Group B for a period of five weeks. This was the second phase in the determination of the dose. A second rest period of four weeks was then instituted, during which the laxative was not given.

Having determined in the two observation periods that 3 grains of either white or yellow phenolphthalein was an effective dose for Group A-1 (constipated, less than 6 years of age), and 2½ grains an effective dose for Group A-2 (constipated, 6 years of age and over), each group was given these doses of white phenolphthalein at three-day intervals for five weeks. As controls, the nonconstipated groups (Group B-1, under 6 years of age; Group B-2, over 6 years of age) were given identical doses of yellow phenolphthalein at similar intervals.

This treatment was followed by a third rest period of three weeks. Then the groups were reversed, Group A receiving yellow phenolphthalein and Group B white phenolphthalein in the same doses as during the previous test period of five weeks. A final observation period of four weeks was used to evaluate the over-all effect of the laxative. The effectiveness of phenolphthalein was determined by the average number of stools of each child per day ("child day").

## RESULTS

### *A. Determination of Dose*

1. *First Phase.*—The daily response to white phenolphthalein, which was given to Groups A-1 and A-2 in doses from 2½ to 3 grains, at three- to five-day intervals, is shown in Table I.

In general, the best response to the laxative appeared within the first twenty-four hours after administration. From small doses, such as 1¾ grains, the effects were not impressive. The occasional increase in the number of stools in the seventy-two-hour period after medication was not taken into consideration in this study, it being understood that the re-excretion of a small quantity of the laxative in the bile produces a gradually diminishing aperient action. The number of stools during the first twenty-four hours was accepted for computing the "base figure," or the average number of stools appearing during the periods of nonmedication, in the orientation phases of the study.

For Group A-1, the base figure without medication was 0.81 stool. The average response in the first twenty-four-hour period was 1.18 after 3 grain doses. For Group A-2, the base figure without phenolphthalein

was 1.83. The average number of stools was 2.03 after 2½ grain doses and 2.01 following 3 grain doses of white phenolphthalein.

On the whole, 3 grains were found to give the best effect in Group A-1 and 2½ grains in Group A-2. It was also noted that there was a tendency for the average number of stools to rise gradually in the seventy-two-hour period during this phase.

not seen in Group B in whom prior to the medication apparently good physiological activity of the intestinal tract existed (Table I).

2. *Second Phase.*—In the second phase of determination of the dose, Group A-1 was started with 2½ grains of yellow phenolphthalein, which was later increased to 3 grains, because of the more pronounced laxative effect of this dose. Group A-2

TABLE I. FIRST PHASE OF STUDY FOR DETERMINATION OF LAXATIVE DOSE: AVERAGE DAILY NUMBER OF STOOLS DURING CONTROL PERIOD, FOLLOWING MEDICATION, AND DURING INTERVALS BETWEEN THE MEDICATION PERIODS

| GROUP | AVERAGE DAILY NUMBER OF STOOLS DURING A THREE-WEEK PRELIMINARY CONTROL PERIOD | SUBSTANCE USED | NUMBER OF TIMES SUBSTANCE WAS GIVEN | | AVERAGE DAILY NUMBER OF STOOLS DURING EIGHT-WEEK TEST PERIOD; PHENOLPHTHALEIN GIVEN AT THREE- TO FIVE-DAY INTERVALS | | |
|---|---|---|---|---|---|---|---|
| | | | | | PHENOLPHTHALEIN | | NO MEDICATION |
| | | | 2½ GR. | 3 GR. | 2½ GR. | 3 GR. | |
| A-1 | 0.81 | White phenolphthalein | 6 | 4* | 1.18 | 1.18*† | 0.81 |
| A-2 | 0.90 | White phenolphthalein | 6 | 4* | 2.03 | 2.01* | 1.83 |
| B-1 | 1.66 | Yellow phenolphthalein | 4 | 4* | 1.57 | 1.62* | 1.22 |
| B-2 | 2.12 | Yellow phenolphthalein | 4 | 4* | 2.14 | 1.98* | 1.96 |

*Number of times the 3 grain dose was given.
†Significant increase in average daily number of stools according to t value.[11]

In the first phase, yellow phenolphthalein, given to Group B-1 (nonconstipated) children in doses of 1 to 3 grains, at two- to five-day intervals, generally produced similar results (Table I). For this group, the base figure was 1.22. Doses of 2½ grains of yellow phenolphthalein raised the average to 1.57 stools in the first twenty-four hours, and 3 grain doses yielded an average of 1.62 stools in the first twenty-four hours. For Group B-2, 1.96 stools was the average number without medication (base figure), 2.14 stools from 2½ grains, and 1.98 stools following the ingestion of 3 grains. The gradual increase in the number of stools in the seventy-two-hour period observed in Group A was

was given 2½ grains of yellow phenolphthalein throughout this phase, while comparable groups of the nonconstipated children were given identical doses of white phenolphthalein.

Without medication, the average for Group A-1 was 1.02 stools. After 2½ grains of yellow phenolphthalein, the average was 1.13, and after 3 grains, 1.30. For Group A-2 the base figure was 1.88, and 2½ grains produced an average of 2.01 stools in the first twenty-four hours after medication. In this instance again, it was noted that the medication had the greatest effect in the first twenty-four-hour period.

For Group B-1 the base figure was 1.40 compared with 1.34 after 2½

grains of white phenolphthalein and 1.51 following the administration of 3 grain doses of yellow phenolphthalein. Group B-2 showed an average of 1.92 stools without medication (base figure) and 2.01 stools after the ingestion of 2½ grains of white phenolphthalein (Table II).

### *B. Consistency of Stools*

Variation in the consistency of the stools, graded as solid, semisolid, or liquid, following the use of phenolphthalein was similar to that present when no laxative was used. Actually, the number of solid stools resulting from the use of phenolphthalein outnumbered the other consistencies at all times.

TABLE II. SECOND PHASE OF STUDY FOR DETERMINATION OF LAXATIVE DOSE: AVERAGE DAILY NUMBER OF STOOLS DURING REST PERIOD, FOLLOWING MEDICATION, AND DURING INTERVALS BETWEEN THE MEDICATION PERIODS

| GROUP | AVERAGE DAILY NUMBER OF STOOLS DURING A ONE-WEEK REST PERIOD | SUBSTANCE USED | NUMBER OF TIMES SUBSTANCE WAS GIVEN | | AVERAGE DAILY NUMBER OF STOOLS DURING FIVE-WEEK TEST PERIOD; PHENOLPHTHALEIN GIVEN AT THREE- TO FIVE-DAY INTERVALS | | |
|---|---|---|---|---|---|---|---|
| | | | | | PHENOLPHTHALEIN | | NO MEDICATION |
| | | | 2½ GR. | 3 GR. | 2½ GR. | 3 GR. | |
| A-1 | 0.91 | Yellow phenolphthalein | 3 | 9* | 1.13 | 1.30* | 1.02 |
| A-2 | 1.74 | Yellow phenolphthalein | 12 | — | 2.01 | — | 1.88 |
| B-1 | 1.15 | White phenolphthalein | 3 | 9* | 1.34 | 1.51* | 1.40 |
| B-2 | 1.85 | White phenolphthalein | 12 | — | 2.01 | — | 1.92 |

*Number of times the 3 grain dose was given.

TABLE III. THIRD PHASE OF STUDY FOR DETERMINATION OF LAXATIVE DOSE: AVERAGE DAILY NUMBER OF STOOLS DURING REST PERIOD, FOLLOWING MEDICATION, AND DURING INTERVALS BETWEEN THE MEDICATION PERIODS

| GROUP | AVERAGE DAILY NUMBER OF STOOLS DURING A FOUR-WEEK REST PERIOD | SUBSTANCE USED | NUMBER OF TIMES SUBSTANCE WAS GIVEN | | AVERAGE DAILY NUMBER OF STOOLS DURING FIVE-WEEK TEST PERIOD; PHENOLPHTHALEIN GIVEN AT THREE-TO FIVE-DAY INTERVALS | | |
|---|---|---|---|---|---|---|---|
| | | | | | PHENOLPHTHALEIN | | NO MEDICATION |
| | | | 2½ GR. | 3 GR. | 2½ GR. | 3 GR. | |
| A-1 | 0.92 | White phenolphthalein | — | 12* | — | 1.29* | 1.15 |
| A-2 | 1.72 | White phenolphthalein | 12 | — | 1.99 | — | 1.83 |
| B-1 | 1.34 | Yellow phenolphthalein | — | 12* | — | 1.56*† | 1.25 |
| B-2 | 1.75 | Yellow phenolphthalein | 12 | — | 1.88 | — | 1.85 |

*Number of times the 3 grain dose was given.
†Significant increase in average daily number of stools according to t value.[11]

Responses similar to those in the first two phases were obtained in the latter two test periods, when 3 grains of either white or yellow phenolphthalein were given to the children under 6 years of age and 2½ grains of the laxatives to those over 6 years of age (Tables III and IV).

### *C. Untoward Symptoms*

1. *Gastrointestinal Manifestations.*—There were no untoward symptoms, such as tenesmus, cramps, flatulence, nausea, or vomiting, after the use of white or yellow phenolphthalein. One

child who complained of abdominal discomfort occasionally was a nonconstipated 2-year-old boy. There were no other complaints.

2. *Skin Manifestations.*—Skin manifestations of idiosynerasy were not seen in any case.

3. *Physical Findings.*—Rheumatic cardiac disease was diagnosed in a phase of the study. The test used for the determination of free phenolphthalein was that described by Fantus and Dyniewiez.[6]

There was no free phenolphthalein, albumin, or any other abnormal constituent in the urine of Group A-1 during the experimental periods.

TABLE IV. FOURTH PHASE OF STUDY FOR DETERMINATION OF LAXATIVE DOSE: AVERAGE DAILY NUMBER OF STOOLS DURING REST PERIOD, FOLLOWING MEDICATION, AND DURING INTERVALS BETWEEN THE MEDICATION PERIODS

| GROUP | AVERAGE DAILY NUMBER OF STOOLS DURING A THREE-WEEK REST PERIOD | SUBSTANCE USED | NUMBER OF TIMES SUBSTANCE WAS GIVEN | | AVERAGE DAILY NUMBER OF STOOLS DURING A FIVE-WEEK TEST PERIOD; PHENOLPHTHALEIN GIVEN AT THREE- TO FIVE-DAY INTERVALS | | | FINAL OBSERVATION PERIOD OF FOUR WEEKS |
|---|---|---|---|---|---|---|---|---|
| | | | | | PHENOLPHTHALEIN | | NO MEDICATION | NO MEDICATION GIVEN |
| | | | 2½ GR. | 3 GR. | 2½ GR. | 3 GR. | | |
| A-1 | 1.17 | Yellow phenolphthalein | — | 12* | — | 1.42* | 1.33 | 1.29 |
| A-2 | 1.85 | Yellow phenolphthalein | 12 | — | 2.00 | — | 1.85 | 1.94 |
| B-1 | 1.30 | White phenolphthalein | — | 12* | — | 1.31*† | 1.11 | 1.15 |
| B-2 | 1.85 | White phenolphthalein | 12 | — | 1.80 | — | 1.70 | 1.90 |

*Number of times the 3 grain dose was given.
†Significant increase in average daily number of stools according to t value.[11]

number of children in each group. None of the children showed any untoward effect from the ingestion of the repeated doses of phenolphthalein.

All children increased in height and weight during this study, in keeping with the normal curve.

Any changes in temperature encountered were due to an intercurrent condition such as upper respiratory infection, otitis media, measles, etc.

### *D. Results of Laboratory Examinations*

1. *Urine.*—The urine of all children was examined for the presence of blood, casts, albumin, sugar, and phenolphthalein before any medication was administered and during each

In Group A-2, free phenolphthalein was found once in specimens from three different persons while they were taking the laxative but was not found on subsequent examinations. In one child, who had asthmatic bronchitis, albuminuria was detected once during an intercurrent upper respiratory infection. No other abnormal urinary findings were noted.

In Group B-1, the urine was normal chemically and microscopically except in three cases. One child with rheumatic heart disease had albumin during a rest period when tonsillitis was an intercurrent infection. This child also showed free phenolphthalein in one instance. Another occurrence of

albuminuria was found during the test period in a child who also had Koplik's spots on physical examination. A third child had albuminuria at one time during the final observation period, when no medication was given.

In the children of Group B-2, the urine was constantly normal, except in two instances. One child with dacryocystitis had albumin in the urine once during the preliminary observation period and continued to show albumin during two medication and two nonmedication periods. Another child had albuminuria in a rest period during the study. No phenolphthalein was found in the urine of any of these patients.

Albumin thus appeared nine times in 495 specimens from children who apparently had no albumin at the beginning of the period of observation. It occurred four times while the children were receiving phenolphthalein and five times during the rest periods. Infections, asthmatic bronchitis, tonsillitis, dacryocystitis, and the finding of Koplik's spots were concomitant in three of these cases. The one patient with albuminuria at the beginning of the study showed traces of albumin during the test periods as well as the rest periods. From these observations, there is no justification to attribute albuminuria to the ingestion of phenolphthalein. This view is in agreement with the findings of Fantus and Dyniewicz,[7] whose study of the subject led them to conclude that medicinal doses of phenolphthalein do not produce albuminuria.

2. *Blood Pressure and Blood Cytology.*—At the beginning and at the conclusion of this study, the ranges in blood pressure, pulse rate, hemoglobin, red blood cell count, white blood cell count, and the ratio of polymorphonuclear cells to lymphocytes were within normal limits, and the number of children showing changes in these respects was within normal expectations.

Complete physical examinations, blood pressure readings, and the blood cytology during all phases of the study showed that repeated doses of white or yellow phenolphthalein, taken over a long period of time, had no untoward effect on the growth and development of the children under observation. Reports have appeared in the literature of cases in which phenolphthalein was said to have produced untoward effects, but the results of this study contradict this finding and appear to be in agreement with the assertion of Vamossy[8] and supported by other observers[9] that phenolphthalein has no immediate or secondary deleterious effect on growth or development or on nervous system, colon, blood, or kidneys.

## DISCUSSION

Conjugated phenolphthalein is always present in the urine of persons taking phenolphthalein, but free phenolphthalein is usually absent, or found only in traces, following medicinal doses. Most of the drug that is absorbed is excreted in conjugated form, and it seems that a certain minimum of conjugated phenolphthalein must be present before free phenolphthalein appears in the urine. Steigmann and Dyniewicz[10] have shown that when conjugated phenolphthalein below 1.9 mg. per cent was present in the urine of normal persons, no free phenolphthalein appeared in the urine.

In the present study, children over 6 years of age were given 2½ grains

and those under 6 years of age 3 grains of white or yellow phenolphthalein. Free phenolphthalein was found only once in four cases during the period of medication (four out of 504 urine examinations), and it did not recur. The effective laxative action in children has evidently prevented the absorption of the drug in quantities sufficient to show free phenolphthalein in the urine.

Fantus and Dyniewicz[6] found that the elimination of conjugated phenolphthalein in the urine reached its peak in the forty-eight-hour period after administration, and in the patients who had cathartic action traces were found for four days. They noted that the amount eliminated in this manner was less than 1.5 per cent of the administered dose, and the greater the cathartic action, the less the amount eliminated in the urine.

Some of the phenolphthalein absorbed is excreted through the bile into the intestine, and, if the amount excreted is adequate, continued stimulation of the intestinal tract is probable. When the quantity absorbed is relatively small, the amount eliminated through the bile into the intestinal tract is correspondingly smaller. The stimulation of the intestinal tract by the small amount of the eliminated drug is slight and may be a factor in the second twenty-four-hour period and to a much lesser extent evident in the third twenty-four-hour period.

Since relatively little phenolphthalein was absorbed by the children under observation, the number of stools passed in the second twenty-four hours may have been due in part to the influence of the phenolphthalein excreted through the bile, but in this study the bowel actions in the third twenty-four-hour period (seventy-two-hour period) were accepted for comparison with the responses to phenolphthalein medication in the first twenty-four-hour period.

As the study progressed there was a gradual rise in the number of stools during the seventy-two-hour period in the constipated groups. This rise was maintained during the rest periods and in the final observation period.

The per cent increases in the number of stools, together with their statistical significance in t-value,[11]* are indicated in the tables by two asterisks. In the constipated group, the per cent increase with medication was lower as the experiment progressed; this was most noticeable in Group A-1. It may be attributed to the fact that though the maximum effect in the first twenty-four-hour period after the administration of the laxatives increased slightly, there was greater relative rise in the number of stools in the course of the seventy-two-hour period. In Group A-1, with yellow phenolphthalein used, only in the second phase of the determination was the increase in stools statistically significant.

The nonconstipated group showed a progressive decrease in response to the laxative in the twenty-four-hour period and in the average number of stools in the seventy-two-hour period of nonmedication. The average number of stools per child day, however, remained well within the normal fig-

*The t value was calculated as follows:

$$t = \frac{\bar{x} - \bar{x}'}{s} \sqrt{\frac{(n' - 1)\ (n_2 - 1)}{n_1 - n_2 - 2}}$$

Level of significance taken as .01, value of t equal 2.5 or probably significant taken as .05 (value of t over 2.0).

ures, and not a single case of constipation occurred.

A comparison of the average number of stools per child day of all the groups during the preliminary observation period with the number of the final observation period showed that the daily eliminations of the constipated groups became similar in quantity and frequency to the nonconstipated groups after the prolonged use of white or yellow phenolphthalein. These results indicate that, besides the immediate laxative effect of phenolphthalein after prolonged use, it changed a constipated child into a nonconstipated child.

The doses of white or yellow phenolphthalein used did not produce purgation, with subsequent absence of bowel movement, but stimulated elimination and eventual return to normal bowel functioning.

A comparison of the laxative efficiency of white and yellow phenolphthalein in all the phases when medication was given shows that in these children the responses produced were within the same range and, therefore, equally effective.

## CONCLUSIONS

1. White or yellow phenolphthalein, in doses of 3 grains at three-day intervals, is an effective laxative for children under 6 years of age. Two and one-half grains of either white or yellow phenolphthalein is an effective laxative dose for constipated children over 6 years of age.

There is no explanation available for the response to lower dosage in the higher age group. It may be due to an intrinsic factor as yet unrecognized.

2. Prolonged use of phenolphthalein in constipated children produced a tendency toward a normal number of stools daily. Nonconstipated children did not become constipated after the prolonged use of phenolphthalein. There is reason to believe that phenolphthalein exerts a "tonic" influence and does not produce dependence on its use.

3. The present study did not reveal significant differences in the laxative effectiveness of white and yellow phenolphthalein during childhood.

4. Phenolphthalein, in the doses administered, had no apparent effect upon the growth and development of children.

5. Phenolphthalein did not produce albuminuria in children.

6. White or yellow phenolphthalein, in 2½ and 3 grain doses, did not produce skin manifestations of idiosyncrasy or any type of allergic reaction in children.

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This study was originally planned and started by the late Dr. M. L. Blatt, Head of the Pediatric Division of the Cook County Hospital.

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# FEVER AND FEBRILE CONVULSIONS IN KITTENS

## A Clinical, Electroencephalographic, and Histopathologic Study

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INTEREST attaches to febrile convulsions in childhood by virtue of the frequency of this complaint[1, 2, 3, 4] and the possible subsequent development of recurrent convulsions without fever. Previous studies indicate the likelihood that brain injury may occur as a result of fever or of convulsions,[3, 5, 6] and that infants are particularly susceptible to this complication. Clinical evidence[1, 7] suggests that cerebral damage incurred in the course of a febrile convulsion is the most important single factor contributing to the development of epilepsy in later life.

It seemed probable, from earlier studies, that electroencephalographic slowing outlasting fever indicates brain injury, and that the duration of the slowing is related to the severity of the damage.[8] Such a relationship between the duration of electroencephalographic slowing and the severity of brain damage has been demonstrated experimentally in kittens.[9] Wegman[10] showed that kittens, like infants, are susceptible to convulsions with fever. In the light of these studies, the kitten seemed a suitable experimental animal to test the thesis that electroencephalographic slowing does, in fact, indicate the presence of cerebral damage incurred during febrile convulsions, and to examine the conditions predisposing to such pathologic changes.

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### MATERIAL AND METHODS

Thirty-two kittens, 2 to 16 weeks old, were studied electroencephalographically before, during, and after a total of forty-nine bouts of artificially induced fever. Unanesthetized kittens were restrained with gauze on a board and placed in a radiant-heating chamber similar to that described by Wegman.[10] Silver cup electrodes containing Sanborn electrode jelly were fastened with collodion to the shaved scalp in bilateral frontal and occipital positions. Interconnected ground electrodes were placed on both ears, and simultaneous scalp-to-ear and scalp-to-scalp recordings were obtained with a six- or eight-channel Grass ink-writing electroencephalograph. The kittens were observed continuously through a window in the chamber. Rectal temperatures and the temperature of the heating box were read at ten- to twenty-minute intervals. In some cases, normal saline was injected subcutaneously in 10 ml. doses at various intervals as indicated by the animal's condition.

The brains of the last nine animals were prepared to allow as clear as

TABLE I

| | AGE IN WEEKS | | | HEIGHT OF FEVER | | DURATION OF EFFERVESCENCE | | FLUID | |
|---|---|---|---|---|---|---|---|---|---|
| | 0-4 | 5-8 | 9-16 | <42.9° C. | >43° C. | <30′ | >30′ | NONE | S. C. SALINE |
| Total | 9 | 32 | 8 | 32 | 16 | 15 | 35 | 21 | 28 |
| Convulsions (number and per cent of total) | 1 (11%) | 8 (25%) | 0 ( 0%) | 3 ( 9%) | 6 (38%) | 8 (53%) | 1 ( 3%) | 2 ( 10%) | 7 (25%) |
| Death with convulsions | 1 | 4 | 0 | 2 | 3 | 4 | 1 | 2 (100%) | 3 (43%) |
| Death without convulsions (number and per cent of total) | 2 (22%) | 3 ( 9%) | 1 (13%) | 2 ( 6%) | 4 (25%) | 1 ( 7%) | 5 (15%) | 2 ( 10%) | 4 (14%) |
| Extreme EEG slowing (number and per cent of total) | 6 (67%) | 14 (44%) | 2 (25%) | 8 (25%) | 4 (25%) | 4 (27%) | 17 (49%) | 13 ( 62%) | 8 (29%) |

possible a demonstration of any microscopic changes. Two of these kittens died during the heating period, and their brains were removed immediately. The remaining seven kittens were sacrificed three days after the last experiment, when neuronal changes would have had time to become evident. The animals were anesthetized with ether and were then bled through a heart stab and perfused with 95 per cent alcohol. The brains were removed immediately and preserved in 95 per cent alcohol. They were then sectioned sagitally and blocks were embedded in celloidin, cut at 20 microns, and stained with toluidine blue by the Nissl technique.

## RESULTS

*Clinical Results.*—

1. *Convulsions* (Table I): The thirty-two kittens were subjected to a total of forty-nine heating periods. On nine occasions, convulsions occurred. Seizures in each instance were generalized and showed the familiar tonic-clonic pattern. A single convulsion lasted 45 to 70 seconds and was followed by failure to respond to external stimuli for less than a minute to as long as an hour. One kitten was semicomatose for four hours after a febrile convulsive episode. Repeated convulsions were the rule. As many as thirty occurred in rapid sequence, separated by 10- to 30-second intervals of coma. Five animals died during the febrile convulsive episode.

The two most important factors determining the occurrence of convulsions were heating time and height of fever. All animals in which the rectal temperature rose above 42.8° C. in less than thirty minutes had a convulsion. The third important factor was the age. The majority of convulsions occurred in kittens 5 to 8 weeks old. None occurred in cats over 8 weeks, and only one kitten under 4 weeks had a convulsion. Finally, the incidence of convulsions was higher when subcutaneous fluids were administered (25 per cent) than when none were given (10 per cent), while the mortality rate was influenced conversely (43 vs. 100 per cent, respectively).

2. *Mortality with convulsions* (Table I): The occurrence of febrile convulsions was attended by a high mortality rate. More than half of the convulsive episodes terminated in death. Death at the time of a febrile convulsive episode occurred in both of the two convulsing kittens which had not received parenteral fluids and in three of the seven which had received saline subcutaneously.

*Mortality without convulsions* (Table I): Fifteen per cent of nonconvulsive febrile episodes terminated in death. The mortality rate was influenced by age, in that it was highest in kittens under 4 weeks of age (22 per cent) and decreased at increasing age levels (10 per cent). The mortality rate was influenced by the height of fever as well, in that death was rare at temperatures below 43° C. Incidence of death due to heat was higher with long effervescence times rather than, as in the case of convulsions, with short effervescence times. The mortality rate without convulsions was not significantly affected by parenteral fluids.

*Electroencephalographic Findings* (Figs. 1 and 2).—

1. *Before heating:* The afebrile EEG was somewhat difficult to assess. The kittens ordinarily were alert with eyes open, and struggling was common, particularly as the temperature rose. Often, however, they fell asleep (less than 10 $\mu$V) activity of indeterminable frequency predominated and was mixed with varying amounts of regular countable waves. As a rule, these were in the 5 to 7 per second range, but some regular countable

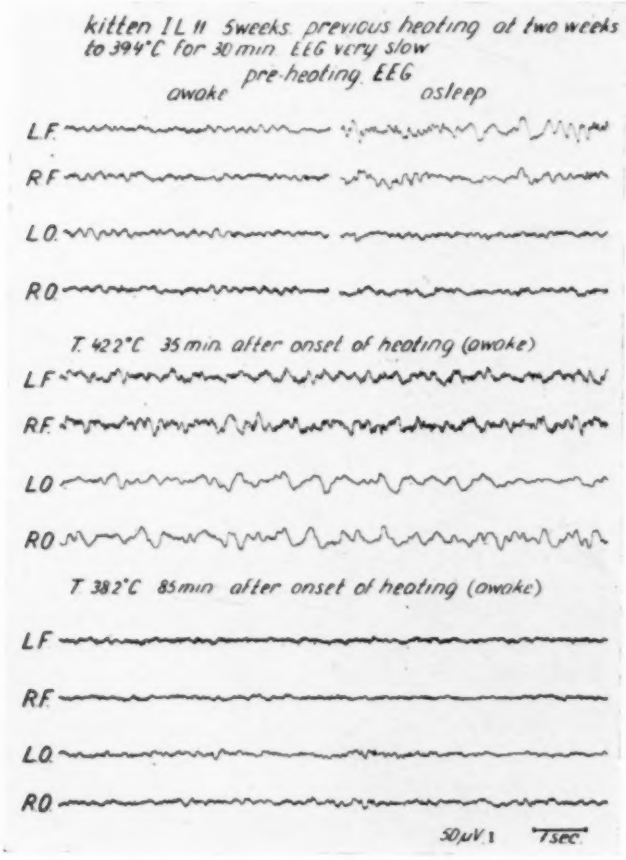


Fig. 1.

and the EEG then showed changes indistinguishable from those of human sleep. In spite of these difficulties, it was possible to see sections during which the animals were awake and quiet. At such times, low amplitude frequencies as high as 12 per second occurred. With increasing age, there was a tendency toward more regular activity at a higher rate, i.e., in the 10 to 12 per second range compared with the 5 to 7 per second range of

the young kittens. The variability was too great, however, and the number of kittens too small to allow a more precise description of the electroencephalogram of kittens and correlation with age. Main reliance was placed on the changes occurring in the individual EEG's with increasing temperature.

in amplitude. Low amplitude activity of indeterminable frequency, so often prominent before fever, disappeared, and long sequences of regular countable frequencies became prominent. With further rise of rectal temperature, the frequency of the regular waves became reduced and there was a further increase in am-

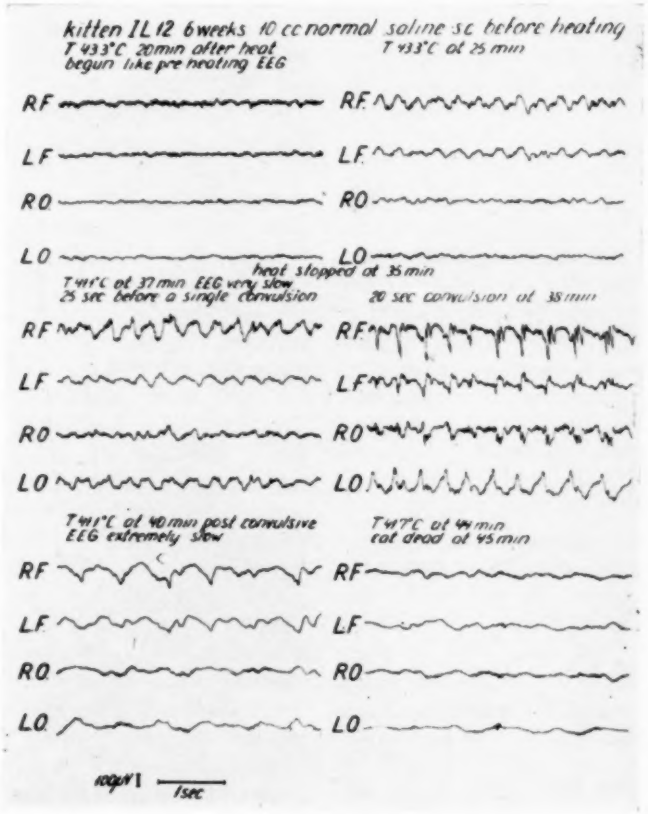
kitten IL 12 6 weeks 10 cc normal saline sc before heating
T 43.3°C 20 min after heat begun like pre heating EEG
T 43.3°C at 25 min
RF
LF
RO
LO
heat stopped at 35 min
T 41°C at 37 min EEG very slow 25 sec before a single convulsion
20 sec convulsion at 38 min
T 41°C at 40 min post convulsive EEG extremely slow
T 41.7°C at 44 min cat dead at 45 min
100 μV
1 sec

Fig. 2.

2 *During fever without convulsions* (Table I, Fig. 1): The sequence of changes, while certainly not uniform, was generally as follows: The first change consisted of a definite increase

plitude. In many records, high (100 μV), smooth 3 to 5 per second waves were continuous at 40 to 41° C.; occasionally, however, they appeared intermittently in runs, inter-

mingled with low amplitude faster frequencies. The record was considered to show extreme slowing when smooth 1 to 3 per second waves predominated in all leads.

Some degree of EEG slowing occurred during fever in all but seven animals. In a few, there was an initial increase in frequency followed by slowing. In general, the degree of slowing varied directly with the height and duration of fever and inversely with age, extreme slowing being most prominent in kittens under 4 weeks of age (67 per cent) and decreasing progressively with increasing age (44 per cent at 5 to 8 weeks, 25 per cent at 9 to 16 weeks). Extreme slowing was twice as common in kittens with an effervescence time of more than thirty minutes (49 per cent) as in those with rapid effervescence (27 per cent). Thus, duration of fever was more closely correlated with the incidence of pronounced EEG slowing than height of fever; marked EEG slowing occurred equally at temperatures below and above 43° C. It was less likely to occur when subcutaneous fluid was given (29 per cent) than when no fluid was given (62 per cent). Return to normal during effervescence was less rapid than the departure from normal with effervescence, but EEG slowing did not outlast fever in any case unless convulsions occurred.

Extreme slowing could not be correlated in time of onset, duration, or cessation with panting. However, to check the possibility that EEG slowing might be due to low blood carbon dioxide content, 5 per cent carbon dioxide in oxygen was administered on five occasions. There was no EEG change except in one kitten in which EEG slowing was accentuated by the inhalation of carbon dioxide.

3. *Electroencephalographic changes with convulsions* (Fig. 2): In almost all instances, convulsions occurred when the EEG had already become extremely slow. During, and sometimes a few seconds before, convulsions, the EEG was characterized by paroxysmal outbursts of fast activity (20 per second) of high amplitude (100 $\mu$V), or more rarely of 3 per second spike and wave formations. After the convulsion, EEG slowing was extreme, roughly for the period of stupor (fifteen to thirty minutes). Marked EEG slowing outlasted defervescence in all animals who convulsed. This marked and prolonged slowing could not be attributed to the convulsion alone since, in our experience, initial electroshock convulsions are followed by slowing which lasts only as long as the stupor.[11] It could not be attributed to fever alone, since slowing did not outlast defervescence in any case of fever without convulsions. Prolonged EEG slowing—as long as twenty-four hours, the longest period it was followed—depended on the combination of fever and convulsions. It was frequently more prominent occipitally than frontally, both with fever alone and after the febrile convulsion.

*Histopathologic Findings.*—The brains of nine animals were available for microscopic study. In four animals no cellular changes were present. Of these kittens, one was normal and one had no EEG slowing, although the temperature had been elevated on two occasions, the last time to 42.7° C. within thirty minutes.

The remaining two kittens with no microscopic brain lesions were the two which died within twenty minutes of beginning temperature elevation, one with convulsions and one w i t h o u t. Presumably insufficient time had elapsed to allow visible neuronal changes to occur.

The brains of three kittens showed striking changes involving both cerebrum and cerebellum. These were the kittens which showed the most marked electroencephalographic slowing. The protocols follow:

Kitten 1, Litter 11, was subjected to fever on two occasions. At the age of 2 weeks a temperature of 39.4° C. was produced within thirty minutes. No convulsion occurred. No fluid was given. The electroencephalogram was very slow during fever. At the age of 5 weeks, a temperature of 42.2° C. was maintained for sixty minutes. No convulsion occurred. No fluid was given. The electroencephalogram was very slow for thirty minutes, and slowing involved the occipital leads more than the frontal. Three days after the last experiment, the animal was sacrificed with ether, perfused with 95 per cent alcohol, the brain removed immediately and preserved in 95 per cent alcohol.

Microscopic examination revealed many shrunken Purkinje cells in the cerebellum and occasional hyperchromatic cells in the pontile nuclei. There were marked cellular changes throughout the cortex, but the most severe changes occurred in the occipital lobes (Figs. 3 and 4). There was marked cellular depopulation, possibly as a result of the first heating experiment. Acute changes consisted of nuclear hyperchromasia and liquefaction of the cytoplasm.

Kitten 5, Litter 11, was heated to 40.6° C. in thirty minutes at the age of 5 weeks. No convulsion occurred and there was no electroencephalographic slowing. The following day it was heated to 42.2° C. in thirty minutes. At the height of fever the animal started to convulse. It was removed from the heating chamber, placed over a cool fan, removed from restraints, and given 20 ml. of saline subcutaneously. In spite of these vigorous restorative measures, it continued to convulse and had approximately thirty 10- to 20-second convulsions within ten minutes. The electroencephalogram continued to be extremely slow, and the kitten remained semicomatose for four hours. Three days later it was sacrificed in the usual manner. The brain showed the most marked cellular changes in the group. Purkinje cells were absent in many folia, and in other areas they were markedly shrunken and hyperchromatic (Figs. 5 and 6). In the cortex, occasional ganglion cells in the frontal lobes showed liquefaction and there was mild microglial reaction. In the parietal and occipital lobes, cells were absent in the different layers so the cortex had a depopulated appearance. The pons and basal ganglions were spared.

Kitten 2, Litter 10, was subjected to temperature elevation to 42.2° C. for sixty minutes and on the following day for eighty minutes. On the second occasion, no fluids were given and fever was accompanied by marked electroencephalographic slowing. The animal was sacrificed three days after the last experiment. The brain showed markedly shrunken and hyperchromatic Purkinje cells and many absent cells. In the occipital lobes were many shrunken hyperchromatic ganglion cells in all layers as well as microglial proliferative reaction. Frontal and parietal lobes, basal ganglions, brain stem and pons were spared.

In two kittens, cellular changes were confined to the cerebellum. The Purkinje cells showed shrinkage and hyperchromasia to a striking degree, but there were no cellular changes in the cerebral cortex, basal ganglions,

Fig. 3.

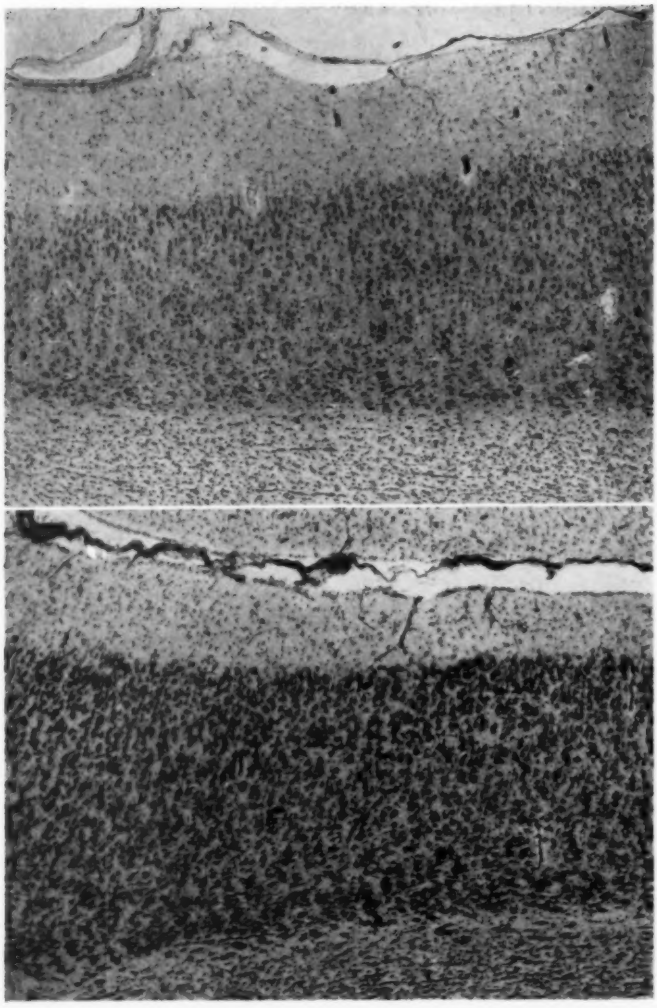

Fig. 4.

Fig. 3.—Kitten 1, Litter 11. Photomicrograph of occipital lobe cortex, showing absence of many neurons and liquefactive changes in others. (Nissl stain; ×220; reduced ⅓.)

Fig. 4.—Normal control kitten of same age as in Fig. 3. Photomicrograph of a comparable region of the occipital lobe cortex to show the normal neuronal population. (Nissl stain; ×220; reduced ⅓.)

Fig. 5.

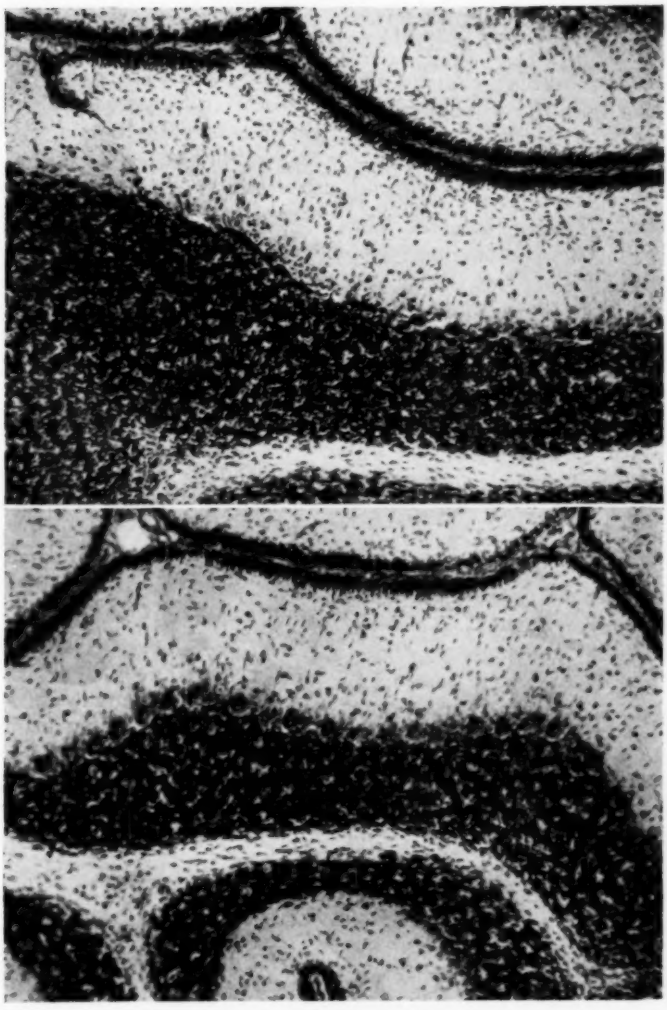

Fig. 6.

Fig. 5.—Kitten 5, Litter 11. Photomicrograph of cerebellar cortex. Note shrunken, elongated, and hyperchromatic Purkinje cells. (Nissl stain; ×220; reduced ½.)

Fig. 6.—Normal control kitten of same age as in Fig. 5. Cerebellar cortex reveals normal round Purkinje cells with distinct nuclei. (Nissl stain; ×220; reduced ½.)

or brain stem. These were kittens subjected to fever of 42.2° C. for thirty minutes at the age of four weeks. Fluids were given and no electroencephalographic slowing occurred.

In summary, cellular changes occurred after both fever and febrile convulsions, and consisted of shrinkage, hyperchromasia, and loss of cells with less frequent microglial reaction. These changes involved the cerebellum most consistently and prominently, then the occipital lobes, and less often the parietal and frontal lobes. Pons, brain stem, and basal ganglions were spared. There was a positive correlation between EEG slowing and the occurrence of cellular pathology both in location and severity of involvement except under two conditions. Kittens which died acutely had marked EEG slowing but no cellular change, presumably because insufficient time had elapsed to allow the development of visible changes. Cellular changes involving only the cerebellum were not manifested by electroencephalographic slowing.

## DISCUSSION

The findings in artificially induced fever in kittens conform to the clinical and EEG findings in human beings[1, 2, 3, 8, 12] and previous clinical findings in kittens.[10] In human beings, febrile convulsions occur predominantly between the ages of 1 to 3 years, are less common before 6 months, and are rare after 5 years. In kittens, convulsions occur predominantly between the ages of 5 to 8 weeks, are rare before, and have not been seen by us after that age. There is no apparent explanation for the special predilection of infants and kittens to respond to fever with convulsions. In cats, on the contrary, fever elevates the convulsive threshold.[13]

By far the most important factors determining the appearance of convulsions in these animals were the height and rapidity of rise of the fever. Rapidity of rise is difficult to determine in human infants, but this factor is probably important, since a convulsion is often the first evidence that the child is sick. A convulsion is said to occur rarely during defervescence[12] and this occurred in one of our experimental animals (Kitten 5, Litter 11). The height of fever at which febrile convulsions are most likely to occur is much lower in infants than in kittens: 39° C. or over for infants, 42.8° C. or over for kittens.

There are no reports on EEG findings during fever in human infants. In human adults, Hoagland[14] reported an increase in frequency with increased fever, and interpreted this to indicate an increase in brain metabolism with fever. Greenblatt,[15] on the other hand, reported slowing with high temperature attributable to hyperventilation. It is not known whether EEG slowing occurs in human infants with fever alone. We have a few cases which suggest that it does. If this is so, then human findings would correspond to the findings in kittens, in whom the degree and incidence of slowing increase with decreasing age. Certainly the occurrence of a convulsion in kittens with fever markedly accentuates and prolongs the degree and duration of slowing out of all proportion to what one would expect to occur after a

convulsion without fever. This corresponds exactly with the situation in human infants, in whom EEG slowing may last as long as ten days after a febrile convulsion. It seems reasonable to assume that a convulsion occurring in the course of a febrile response may interfere so gravely with cerebral circulation as to allow anoxic changes to develop. Such an interpretation is consistent with the pathologic changes reported in children dying within hours or days of a febrile or febrile-convulsive episode.[3, 5, 6] It is possible that the thermal death time of infant brain is shorter than that of adult brain, and that this may explain the increased susceptibility to brain injury with decreasing age.

The close correspondence between electroencephalographic slowing and microscopic changes confirms the clinical impression that electroencephalographic slowing in children with febrile convulsions does in fact mirror pathologic changes. The return of the electroencephalogram to normal does not indicate that the cellular changes are reversible but only that the damaged cells have disappeared, or at least no longer influence the electrical activity of the remaining normal neurones.

Prevention of brain damage depends on prevention of excessive fever, maintenance of an adequate circulation during fever by administration of fluids, and prevention of convulsions. These measures are particularly imperative in infants, especially under 3 years of age. Since the cerebral pathology incurred in the course of a febrile convulsion seems to be the most important single factor contributing to the development of epilepsy in later life, it follows that the prevention of febrile convulsions is a preventive measure, the only practical one in the field of epilepsy today.

## SUMMARY AND CONCLUSIONS

1. Thirty-two kittens were subjected to elevation of temperature by external heat in forty-nine experiments. Electroencephalograms were obtained before, continuously during, and after fever. The last nine kittens were sacrificed and the brains examined histologically.

2. Clinical findings conformed closely to findings in human beings. Convulsions occurred primarily between the ages of 5 and 8 weeks and were determined primarily by height and rapidity of rise of the fever. Mortality was highest when convulsions occurred, when fever was prolonged, and in kittens of 4 weeks or younger. Mortality was reduced in kittens given parenteral fluids.

3. Electroencephalographic slowing occurred during the fever most frequently in kittens 4 weeks or younger, was most pronounced with prolonged fever, but did not outlast defervescence unless convulsions occurred. When convulsions occurred, slowing was markedly accentuated and lasted as long as twenty-four hours—the longest period it was followed. When slowing occurred, it tended to be more prominent posteriorly than anteriorly. It occurred significantly less often when subcutaneous fluids were given than when such treatment was withheld during the fever.

4. Cellular changes were closely correlated in location and severity

with electroencephalographic slowing. Changes consisted of hyperchromasia, shrinkage, and loss of neurons, and involved the cerebellum most prominently and consistently, then the occipital lobes. The frontal and parietal lobes were less often involved and the basal ganglions, pons, and brain stem were spared. Kittens that died acutely showed electroencephalographic but no cellular changes, and two kittens with cellular involvement confined to the cerebellum did not show corresponding electroencephalographic slowing.

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# A STUDY OF EARLY AND LATER INTRODUCTION OF SOLIDS INTO THE INFANT DIET

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THERE is a marked difference in the practices of introducing solid food into the diets of infants. This has been obvious to all who work in the field of child health and nutrition. Some infants are started on solids one or two weeks after birth and by four to six weeks are deriving a considerable portion of their food requirement from this source. On the other hand, an almost equal number are not receiving the addition of solid foods until approximately 3 months of age, with a slower increase in the amount added.

Those interested in optimal growth and development of the infant are concerned whether one method actually has greater influence on the infant's progress than the other. Also, though in many cases the early feeding process appears to go quite smoothly for both mother and child, sometimes the infant does not respond well to the procedure. If this causes a great deal of concern to the mother the question is raised as to whether she should be encouraged to continue the unhappy process or advised to cease her efforts entirely for a time. The added cost and extra preparation involved is also of concern to many families.

Consequently, an analysis of the effect of early or later feeding of solids on the general state of some normal infants seemed indicated. A large number of infants are seen for well-child supervision at the University of Washington Child Health Center, a well-child clinic located in the student housing project of the University of Washington. All children are followed for the duration of the parent's school period, which is usually several years, and attention is paid to all aspects of the child's growth and development. It was felt that with such a group of infants a study might be made which would help clarify some points in regard to benefits from early or later solid feeding.

With these thoughts in mind we attempted a study of the progress of two groups of infants: one receiving solid food quite early; the other receiving only breast milk or formula and supplementary vitamins for the first three months of life and then a gradual introduction of solid foods into the diet.

All infants included in the study were enrolled between the ages of 1 and 4 weeks for well-child supervision at the Child Health Center. Whether each baby was to be an early or later feeder was determined for the most part by the mother or by the baby's private physician. The

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Center staff accepted these feeding schedules and sorted the infants into the early or the later feeding group. A total of eighty-five infants participated in the project. Whenever possible a child was followed for a year, but if a baby was observed for at least six months he was included in the study. Table I shows the number of months subjects in the two groups were studied.

While infants were classified only according to feeding schedules, an attempt was made to determine that the two groups were similar in regard to other important factors.

Therefore it was considered important to analyze the prenatal diets of the mothers so that this factor could be considered if necessary. In an interview the nutritionist obtained a prenatal diet history from each mother. These diets were evaluated for calories, protein, iron, calcium, vitamin A, ascorbic acid, and vitamin D. Seventy per cent of the recommended daily allowances for the pregnant woman was considered adequate. Anything below this figure was considered inadequate. Evaluation of these prenatal diet histories showed that fourteen mothers of infants in the early group and ten mothers of infants in the later group consumed inadequate diets. Thus, approximately one-fourth of the prenatal diets evaluated did not meet prescribed standards.

In comparing the ages of the mothers we found that the average age was 25 years for the later feeding group and 26 for the earlier. Twenty of the babies in the later group and twenty-four of the earlier group had siblings. Twenty-eight of the infants in the later feeding group and twenty-four of the early feeding group were breast fed. In addition, the number of months each infant was breast fed was very similar for the two groups as shown in Table II.

TABLE I. LENGTH OF TIME SUBJECTS IN BOTH GROUPS PARTICIPATED IN STUDY

| | MONTHS | | | | | | | TOTAL NUMBER PARTICIPATING IN STUDY |
|---|---|---|---|---|---|---|---|---|
| | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Number of subjects in early group | 2 | 3 | 2 | – | 5 | 4 | 29 | 45 |
| Number of subjects in later group | 2 | 3 | 6 | 1 | 3 | 3 | 22 | 40 |

TABLE II. LENGTH OF TIME INFANTS WERE BREAST FED IN THE TWO GROUPS

| | NUMBER MONTHS BREAST FED | | | | | | | | | | | | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Later feeding | 2 | 5 | 4 | 3 | 3 | 2 | 2 | 3 | 2 | 3 | 2 | 0 | 31 |
| Early feeding | 3 | 5 | 4 | 5 | 1 | 1 | 1 | 1 | 1 | 2 | 0 | 0 | 24 |

Infants in both groups were either breast fed or given formulas plus multivitamins and orange juice from birth. The difference between the two groups was the introduction of solids during the first four weeks in the early feeding program while the introduction of solids was made during the ninth to twelfth week period in the later schedule. Table III shows the approximate time of introduction for various foods for each group.

In order to measure progress of the babies the following procedures were used: Each infant received monthly (1) a physical examination by one of the Child Health Center staff pediatricians; (2) hemoglobin and red blood cell determination using a Leitz-Rouy Photrometer; capillary blood was obtained from freely punctured wounds of the heel or great toe; (3) measurements of height and weight and analysis of growth as shown by pattern on the Wetzel Grid.

The nutritionist obtained dietary histories at ages 3, 6, 9, and 12 months for each infant. These were evaluated for calories, protein, calcium, iron, vitamin D, vitamin A, thiamine, riboflavin, niacin, and ascorbic acid, judged on the basis of 50 calories per pound and 1.5 Gm. protein per pound for adequacy. The recommended daily dietary allowance for the other nutrients for infants was considered adequate for the remaining nutrients.

In the interviews which the pediatrician and nurse conducted with the mother at the time of each visit to the clinic a history of any feeding difficulty such as food refusals, number of foods disliked, vomiting, diarrhea, and spitting up was recorded.

For purposes of tabulation a "food refusal" was defined as rejection of a certain food for a period of at least two weeks when several attempts were made to reintroduce the food into the diet.

## RESULTS

As shown in Tables IV and V, 419 hemoglobin and red blood cell determinations were made on the blood samples of forty-five infants in the early feeding group and 382 hemoglobin and red blood cell determinations were made on the blood samples of forty infants in the later feeding group.

There was the greatest difference during the first four weeks in the mean hemoglobin level between the two groups with a difference of 0.21 Gm. per 100 ml. The early feeding group had a mean hemoglobin level of 13.72 and the later group 13.93 for the first four weeks. Lowest differences in the mean hemoglobin levels of 0.02 Gm. per 100 ml. were during the twenty-fifth to twenty-eighth week period. During this period the mean hemoglobin level for the early group was 11.04 as compared with 11.06 for the later group. A further comparison of the mean hemoglobin values with the number of determinations and age in weeks for the early

TABLE III. TIME OF INTRODUCTION OF VARIOUS SOLIDS FOR EACH GROUP

| FOOD | LATER GROUP | EARLY GROUP |
|---|---|---|
| Multivitamin preparation | 2 wk. | 2 wk. |
| Orange juice | 2 wk. | 2 wk. |
| Cereal, precooked | 3 mo. or later | 0-4 wk. |
| Fruits, strained | 4-5 mo. | 1-2 mo. |
| Vegetables, strained | 4-5 mo. | 1-2 mo. |
| Meat, strained | 6 mo. | 1-3 mo. |
| Egg yolk | 6 mo. or later | 4 mo. |
| Cottage cheese, Fish, Yellow cheese, Toast, White potato | 6-12 mo. | 5-10 mo. |

and later groups may be seen in Table IV.

The scatter graph Fig. 1 shows the spread of hemoglobin values and mean hemoglobin level of infants from both groups. As shown, the range of values in both groups was

In analyzing the mean red blood cell determinations we find the greatest difference during the forty-fifth to forty-eighth week period. The early feeding group had a mean red blood cell level of 4,345,240 cells per cubic millimeter as compared with

TABLE IV. COMPARISON OF THE MEAN HEMOGLOBIN VALUES WITH NUMBER OF DETERMINATIONS AND AGE IN WEEKS FOR EARLY AND LATER GROUPS

| | EARLY | | LATER | |
|---|---|---|---|---|
| AGE (WK.) | NUMBER OF DETERMINATIONS | HEMOGLOBIN GM./100 ML. (MEAN) | NUMBER OF DETERMINATIONS | HEMOGLOBIN GM./100 ML. (MEAN) |
| 0-4 | 35 | 13.72 | 36 | 13.93 |
| 5-8 | 41 | 11.33 | 37 | 11.47 |
| 9-12 | 40 | 10.88 | 38 | 11.00 |
| 13-16 | 39 | 11.30 | 39 | 11.11 |
| 17-20 | 39 | 11.13 | 36 | 11.28 |
| 21-24 | 42 | 11.20 | 36 | 11.31 |
| 25-28 | 34 | 11.04 | 34 | 11.06 |
| 29-32 | 30 | 11.18 | 32 | 11.25 |
| 33-36 | 30 | 11.13 | 25 | 11.18 |
| 37-40 | 29 | 11.30 | 26 | 11.42 |
| 41-44 | 31 | 11.11 | 21 | 11.16 |
| 45-48 | 29 | 11.18 | 22 | 11.31 |

TABLE V. COMPARISON OF THE MEAN RED BLOOD CELL VALUES WITH NUMBER OF DETERMINATIONS AND AGE IN WEEKS FOR EARLY AND LATER GROUPS

| | EARLY | | LATER | |
|---|---|---|---|---|
| AGE (WK.) | NUMBER OF DETERMINATIONS | RBC/CU. MM. (MEAN) | NUMBER OF DETERMINATIONS | RBC/CU. MM. (MEAN) |
| 0-4 | 35 | 5,448,570 | 35 | 5,366,860 |
| 5-8 | 41 | 4,569,750 | 37 | 4,641,620 |
| 9-12 | 40 | 4,429,750 | 37 | 4,458,910 |
| 13-16 | 38 | 4,539,470 | 39 | 4,382,300 |
| 17-20 | 39 | 4,495,380 | 36 | 4,446,380 |
| 21-24 | 42 | 4,506,820 | 36 | 4,445,550 |
| 25-28 | 34 | 4,474,700 | 33 | 4,409,690 |
| 29-32 | 30 | 4,423,330 | 32 | 4,409,680 |
| 33-36 | 30 | 4,429,000 | 25 | 4,376,400 |
| 37-40 | 29 | 4,536,550 | 26 | 4,481,150 |
| 41-44 | 31 | 4,360,320 | 29 | 4,372,750 |
| 45-48 | 21 | 4,345,240 | 22 | 4,587,720 |

greatest the first four weeks of life. The hemoglobin range for the first four weeks was 10.6 to 17.95 for the early group and 10.6 to 16.8 for the later group. From the ninth to twelfth week through the forty-eighth week there was a narrowing of the range to 10 to 12 Gm. with the mean falling consistently around 11 Gm. hemoglobin per 100 ml.

4,587,720 cells per cubic millimeter for the later group. The lowest mean difference was between the twenty-ninth- and thirty-second-week period with a cell count of 4,423,330 for the early group and 4,409,680 for the later group. Further tabulations of the mean red cell values with the number of determinations and age in

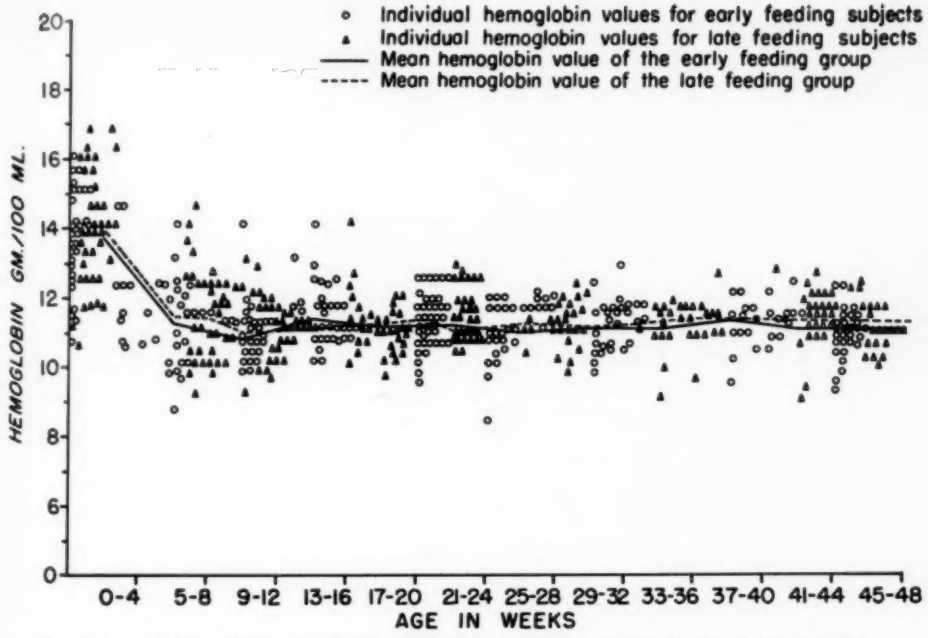


Fig. 1.—A scatter pattern of the 801 hemoglobin values of infants in the early and later feeding groups.

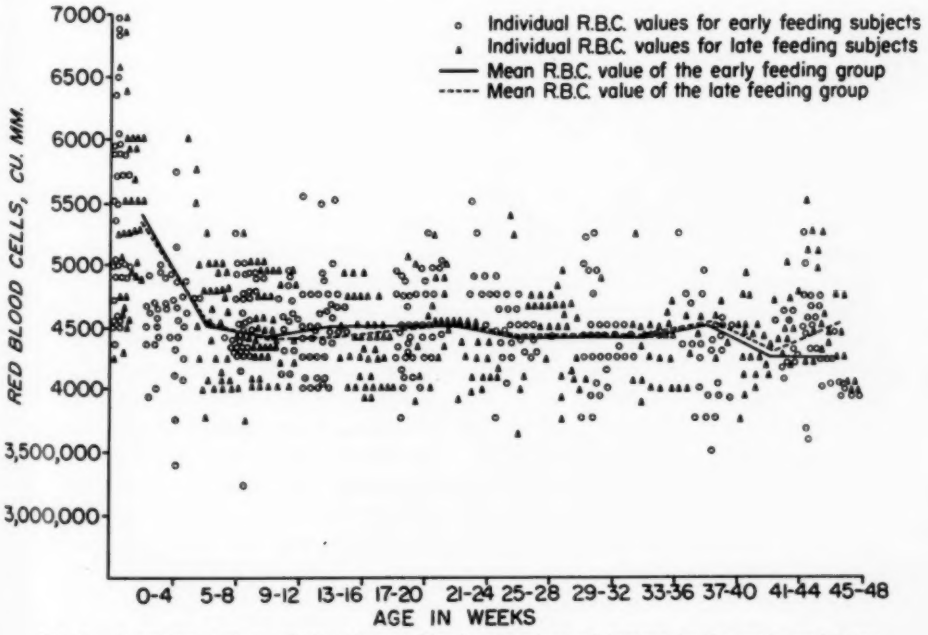


Fig. 2.—A scatter pattern of the 801 red blood cell values of infants in the early and later feeding groups

weeks of all infants are given in Table V.

The scatter graph Fig. 2 shows the spread of red blood cell values and mean red blood cell values of infants from both groups. Again the range of values in both groups was greatest the first four weeks of life. Values ranged from 4,300,000 to 7,400,000 for the early group as compared with 4,470,000 to 7,400,000 for the later group. From the ninth to twelfth week through the forty-eighth week there was a narrowing of the range with the majority of values between 4,000,000 and 5,000,000 red cells per cubic millimeter.

lated for study. Definitive data for the 0 to fourth week period and forty-fifth to forty-eighth week period are given in Table VI.

The Wetzel Grid was used as our measurement for evaluating growth of the infant. A baby was considered in growth failure if there was more than a five level lag from his established auxodrome. For purposes of this study obesity was not considered abnormal. Two subjects in the later feeding group became obese in the latter quarter of the first year.

Of our early feeding group thirty-six infants showed satisfactory growth and nine unsatisfactory growth. In

TABLE VI. MEANS, STANDARD DEVIATIONS, AND STANDARD ERRORS OF MEANS FOR THE TWO GROUPS OF INFANTS FOR HEMOGLOBIN AND RED BLOOD CELL DETERMINATIONS

| WEEK | GROUP | HEMOGLOBIN (GM./100 ML.) MEAN | HEMOGLOBIN (GM./100 ML.) S.D. | RED BLOOD CELLS (CU. MM.) MEAN | RED BLOOD CELLS (CU. MM.) S.D. | S.E. OF MEAN | NUMBER OF DETERMINATIONS |
|---|---|---|---|---|---|---|---|
| 0-4 | Early | 13.72 | 1.37 | | | 0.235 | 35 |
| 0-4 | Later | 13.93 | 1.67 | | | 0.283 | 36 |
| 45-48 | Early | | | 4,345,240 | 349,000 | 65,900 | 21 |
| 45-48 | Later | | | 4,587,720 | 457,300 | 99,800 | 22 |

The means for the 0 to fourth week period and the forty-fifth to forty-eighth week period have been calculated for both hemoglobin and red blood cell values. These two periods were selected because these were the periods of greatest deviation between the two groups with respect to the hemoglobin and red blood cell values.

The mean difference for hemoglobin and red blood cell values between the two groups for each of the above-named periods was subjected to the t test of significance. The results indicated no significant difference exists for the hemoglobin and red blood cell levels in either period. The distribution of mean differences was essentially the same for all the periods iso-

the later feeding group thirty-one showed satisfactory growth and nine unsatisfactory growth. This means that approximately 80 per cent of infants of each group showed satisfactory growth.

In all cases of growth failure dietary analysis revealed an inadequate intake during the period and immediately preceding the growth lag. Seventeen of the eighteen subjects in growth failure were not consuming sufficient calories for optimal growth. In the following order protein, calcium, iron, and ascorbic acid intakes were found to be below prescribed standards. Further study of the individual growth failures in each case shows some possible basis for the poor

growth and low intake. In the early feeding group four had a history of moderate or severe illness during the first year, one with an extreme case of eczema being treated through dietary restriction; one had severe diarrhea, and three had a history of many food refusals. The later feeding group showed similar findings with two subjects showing an unusual number of illnesses; one had an extreme case of eczema; and three had a history of many food refusals. One infant had an inadequate intake owing to diminished breast milk supply. At first this mother refused to give up breast feeding and offer a bottle, and during this time the infant went into growth failure.

Also four subjects who were growing poorly showed an extreme degree of fearfulness during the pediatric examination. One infant showed a history of extreme night awakening over a period of several months. Two infants had growth lags when the mothers went back to work without providing consistent child care programs for the infants. These factors perhaps can be taken as an indication of some adjustment disturbance which in turn might hinder a child's attaining his optimal growth.

Evaluation of the prenatal diet histories as explained previously revealed that fourteen mothers of infants in the early group and ten mothers of infants in the later group consumed diets that were below two-thirds the recommended daily allowance set for the pregnant woman.

Evaluation of these poor diets revealed twelve were only slightly below two-thirds, seven about one-half, and five less than one-third the recommended daily allowance for protein, calories, iron, calcium, and ascorbic acid.

The mean hemoglobin level of infants from mothers with an adequate versus an inadequate prenatal diet was 14 as compared with 13 in the early feeding group; 14 as compared with 13 7/10 in the later feeding group. The hemoglobin range of the five infants from mothers consuming less than one-third the recommended daily allowance was 11.6 to 15.15. Thus, since there was practically no difference in the hemoglobin levels of the two groups and since there was no anemia found in any infants, the maternal diets must have been sufficiently adequate for good fetal development. Smith[1] stated that the duration of maternal nutrition deficiency is an important factor in determining whether or not the maternal nutritional status will influence the developing fetus, and long-term malnutrition may be a more important factor in fetal development than brief periods of actual starvation. Similarly there is a need for more knowledge as to the role of specific nutrients as contrasted with over-all general undernutrition in maternal nutrition. Guest[2] and Niccum and associates[3] showed that if the prenatal diet supplied an adequate amount of iron and other nutrients, an iron deficiency anemia in full-term infants free of infections during the first year is rare.

The early feeding group showed four subjects with a great many and five with a moderate number of illnesses in the first year. The later feeding group revealed two subjects with a great many and four with a moderate number of illnesses. Thus,

the two groups had a comparable number of illnesses during the first year.

The addition of solids into the diet during the first month or two did not seem to change the character of the stools nor the number of stools. Both groups showed great variability in the number of stools. Some children had one bowel movement for every feeding, others one bowel movement every three days. This variability continued throughout the first year with some moderation of the extremes.

There were four cases of moderately severe diarrhea in the early group and three cases in the later group. The number of cases of diarrhea unassociated with infection was approximately the same for both groups.

There was no significant difference in the amount of constipation, colic, excessive regurgitation, or night awakening between the two groups.

Seven cases of eczema were noted in the early feeding group and three in the later feeding group. No attempt was made to associate these with food allergy. In each case, however, there was a family history of either food allergy, hay fever, asthma, urticaria, or eczema. Of the thirty-eight infants in the early feeding group without eczema seventeen had a positive family history of allergy. Of the thirty-eight infants in the later feeding group without eczema twenty had a positive family history of allergy.

The number of food refusals between the two groups was approximately the same. Similarly the number of foods accepted into the diet was approximately the same. By the twenty-eighth week both groups had accepted fruit, vegetables, cereal, meat, yolk, orange juice, and vitamins into their diet. Consequently, one might venture to say that the time of the addition of solids into the infant diet does not seem to affect the degree of acceptance of solids.

## SUMMARY AND CONCLUSIONS

A study was made of the progress of eighty-five infants from a homogeneous background divided into two groups designated as early and later feeding. Infants in both groups were either breast fed or given formulas plus multivitamins and orange juice from birth. Solids were introduced in the early feeding group during the first four weeks of life and in the later feeding group during the ninth to twelfth week age period.

Four hundred and nineteen hemoglobin and red blood cell determinations were made on the blood samples of forty-five infants in the early feeding group and 382 hemoglobin and red blood cell determinations were made on the blood samples of forty infants in the later feeding group. The t test of significance applied to the mean hemoglobin and red blood cell determinations for the months of greatest deviation between the two groups reveals no significant difference. After the third month the mean hemoglobin value was around 11 Gm. per 100 ml.

Growth between the two groups was comparable, as was the number of illnesses, character of the stools, number of stools, incidence of diarrhea, constipation, colic, excessive re-

gurgitation, and number of food refusals.

The authors are grateful to the Staff of the Child Health Center for their help in this study.

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# AN IMPROVED INDWELLING TUBE FOR FEEDING PREMATURE INFANTS

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IN THE July, 1952, JOURNAL[1] we presented a method of feeding premature infants by means of an indwelling polyethylene tube. The technique, originated in this department and in use since January, 1950, was described, and indications for its use were outlined. This method has been favorably received as indicated by communications from various clinics in this country and abroad and by the comments of our own staff.

Since the publication of this procedure, articles have appeared suggesting modifications in the treatment of the polyethylene tube to lessen the possible traumatization of the mucous membrane of the pharynx, esophagus, and stomach when the tube is improperly introduced. Paraffining or flaming the end of the tube, sealing the end, and cutting openings in the side near the end have been advocated.

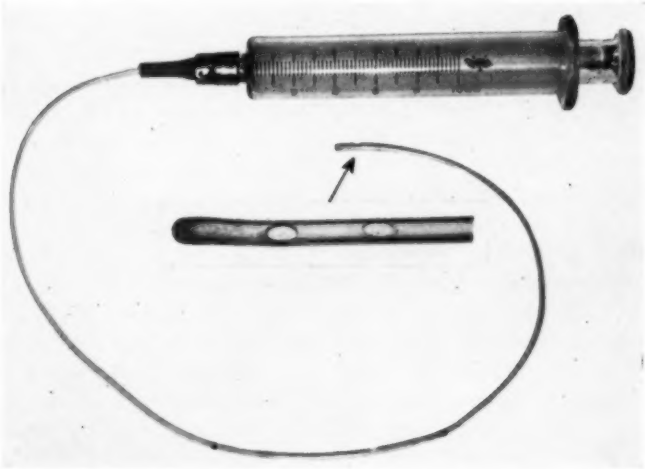

Fig. 1.—Polyvinyl tube, adaptor, syringe, and photomicrograph of blunt tip with holes.

We have felt that the polyethylene tube is neither as soft nor as flexible as it should be and that the cut end is comparatively sharp. Fraying of the external end occurs after a short period of use. Our attention recently has been called to a specially formu-

From the Premature Service of the Cincinnati General Hospital and the Department of Pediatrics, College of Medicine, University of Cincinnati.

lated polyvinyl-type plastic tube* that meets all the requirements for a safe indwelling gastric tube. Although soft and pliable, this tube presents no difficulty in passage through the nares into the stomach. The gastric end of the tube is closed and rounded, and there are openings in the side near this end. The opposite end has a plastic adaptor attached to it which accommodates the tip of the syringe containing the formula, thus eliminating the needle that was inserted in the end of the tube for reception of the syringe tip.

The tube is marketed in a sterile plastic container ready to use. It can, however, be sterilized by cold sterilizing solutions, by boiling, or by autoclaving. We have found that the tube does not deteriorate or fray readily, and there has been no evidence of mucous membrane irritation. Various sizes of this tube are available, the F No. 5 being the one best suited for feeding premature infants.

Our experience with this type of tube has been favorable, and its advantages over the polyethylene tube are so obvious that we recommend its use as a distinct improvement in the technique of the indwelling tube method of feeding premature infants.

*Pharmaseal Laboratories, Inc., 1015 Grandrum Ave., Glendale, Calif.

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# PROCEDURE FOR STERILIZING AND STORING POLYETHYLENE CATHETERS

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DIAMOND[1] introduced the technique for performing replacement transfusions in newborn infants through the umbilical vein. This method and its modifications[2] require the use of polyethylene tubing, which is also used in administering continuous intravenous infusions to older children and adults. Unfortunately this type of plastic tubing cannot be sterilized by boiling, autoclaving, or immersion in alcohol or formalin. Diamond and associates[3] have recommended sterilization by immersion in 1:1,000 aqueous Zephiran in a monel-metal cannister for at least eighteen hours.

We have found this procedure to be efficient but inconvenient because our equipment is used in various hospitals within a radius of thirty miles. We have developed a simple way to store our catheters so that they can be kept in readiness and transported conveniently with no danger of contamination.[4] Over 250 of these packaged catheters have been used in performing exsanguination transfusions in infants over the past five years without a single instance of infection.

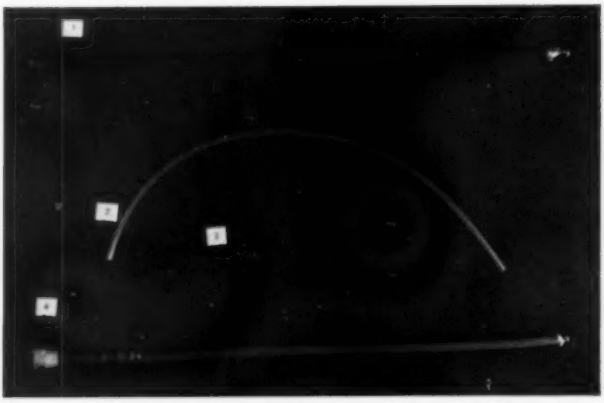

Fig. 1.—Method for sterilizing and storing polyethylene tubing. See text for description.

## METHOD (FIG. 1)

1. Glass tubing (outside diameter 8 to 9 mm.) is cut into 11 inch lengths. One end is sealed in a Bunsen flame and the open end is fire-polished.

*Medical Director of the Junior League Blood Center of Milwaukee, and Assistant Clinical Professor of Medicine, Marquette University School of Medicine.

2. The polyethylene tubing* is cut into 10 inch lengths and placed into the prepared glass tubes, which are then filled with 1:1,000 aqueous Zephiran chloride.† The lumen of the plastic catheter fills automatically if held perpendicularly.

3. The open ends of the glass containers are closed with hooded serum vial stoppers‡ which are further secured with adhesive tape.

The polyethylene catheters may be kept in these containers indefinitely.

*We have found tubing of internal diameter 0.062 inch which slips on a 15 gauge needle best for routine use. Supplied by Clay-Adams Company, Inc., New York, Catalog No. PE205.

†Benzalkonium chloride, U.S.P. Distributed by Winthrop-Stearns, Inc., New York.

‡Obtainable from Glasco Products Co., Chicago, Catalog No. 120C.

SUMMARY

A simple method for sterilizing and storing polyethylene catheters has been presented.

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# PERIORBITAL EDEMA AS THE INITIAL SIGN OF INFECTIOUS MONONUCLEOSIS

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NEW YORK, N. Y.

CASE REPORT

A. M., a 12-year-old school girl previously well, came home from school at 6 o'clock feeling hot and tired and was found to have a rectal temperature of 104.8° F. She was seen by me two hours later when she appeared flushed and acutely ill. The most striking feature of her examination was the condition of her eyelids and periorbital tissues, which though not reddened were definitely puffy so that her eyes looked small, and her mother commented on her changed facial appearance. There was no conjunctivitis and no tearing. There was no tenderness over the antra or ethmoid sinuses. The buccal mucosa and the throat looked normal. The tonsils were not inflamed and showed no exudate. There was no peripheral edema except about the eyes. The remainder of the examination was completely negative. No superficial lymph nodes could be palpated. The liver and the spleen could not be felt. The heart and lungs were normal. There was no eruption. Neurological examination was negative. A urine specimen was obtained and proved normal.

The child's past history was noncontributory. There was no history of her having eaten pork and there was no personal or familial history of allergy. The girl had taken no drugs nor had she eaten any unusual foods. She had received no recent injections.

On the basis of the clinical findings, the normal urine, the negative allergic history, and the denial of pork having been eaten, infectious mononucleosis was suspected.

Address: 1097 Park Avenue.

The following morning the physical findings were unchanged, but the temperature had dropped to 103° F. No lymph nodes could be felt nor was the spleen palpable. A blood spread taken at this time showed the typical findings of infectious mononucleosis. That afternoon small, shotty lymph nodes appeared in the posterior cervical region, and the following day the anterior cervical and axillary nodes became enlarged and the spleen became palpable. Coincidentally, a gray, heavy, confluent exudate appeared on both tonsils. A throat culture failed to show diphtheria bacilli. The periorbital edema gradually disappeared in the course of five days. The fever disappeared by lysis in the course of a week, and the child made an uneventful recovery.

The following blood counts taken by a hematologist (Dr. Nathan Rosenthal) corroborated the diagnosis of infectious mononucleosis.

On the second day of illness, the hemoglobin was 12.0 Gm. (77 per cent); red blood cells 3,590,000; white blood cells 12,400; platelets 190,000; polynuclear band forms 7 per cent; polynuclear segmented forms 14 per cent; lymphocytes, normal 10 per cent, atypical 64 per cent; monocytes 4 per cent; plasmacytes 1 per cent.

On the ninth day of illness, the hemoglobin was 13.0 Gm. (83 per cent); red blood cells 5,150,000; white blood cells 7,750; platelets 260,000; polynuclear band forms 8 per cent; polynuclear segmented forms 15 per cent; polynuclear basophil 1 per cent; lymphocytes, normal 69 per cent, atypical 6 per cent; monocytes 1 per cent; heterophil agglutination 1:32.

Later blood counts were normal.

## DISCUSSION

In 1933 I observed two cases of infectious mononucleosis, one in a girl of 5 years and one in a boy of 14 years in whom the first signs of disease were fever and periorbital edema. At that time I could find no mention of this manifestation in the literature. Since then I have seen four more instances of this sign. The first mention in the literature of its occurrence is in a review of infectious mononucleosis by Alan Bernstein in 1940.[1] This author said, "Puffiness of the eyelids, sometimes referable to edema of the lids, appeared at the onset of one of our recent cases. Although not seen as frequently, it may be as striking as is observed in trichiniasis." Except for this instance this symptom is not mentioned in the comprehensive reviews of infectious mononucleosis[2] until 1945 when Milne,[3] reporting on 111 cases of mononucleosis in young adults, wrote, "The eye symptoms were unusual. Three patients presented watery eyes as the only early complaint and two others noted marked puffiness of the lids." In 1951, in a review of 210 cases of mononucleosis observed at the Mayo Clinic, Stevens and associates[4] reported edema of the eyelids in 6.6 per cent of their cases.

The eyes may be involved both at the onset and during the course of mononucleosis. Follicular conjunctivitis with edema of the lids lasting two days has been described as initiating the disease,[5] and Glanzmann[6] mentioned that dullness and a sleepy look of the eyes are characteristic. Involvement of the retina with papilloretinal edema has been described by several observers and has been attributed to the neurotropic characteristics of the virus, even where lumbar puncture revealed normal spinal fluid.[7] In one such case[8] retinal changes with acute reduction of vision was the initial symptom of the disease.

The cause of the lid edema is obscure. It may be due to lymphatic obstruction even if no peripheral lymph nodes are palpable. In the cervical adenopathy accompanying mononucleosis, periglandular edema is commonly noted,[9] probably as part of the inflammatory process, but it should be stressed again that the edema about the eyes is not accompanied by signs of inflammation.

## SUMMARY

Attention is called to the presence of periorbital edema without obvious cause as the initial sign of infectious mononucleosis. A typical case is presented. Early recognition of this symptom may be helpful in making a rapid diagnosis of this disease.

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# RENAL HAMARTOMA

## Report of a Case Diagnosed Ante Mortem

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A REPORT of a case of isolated renal hamartoma, diagnosed ante mortem, in a 3-month-old infant is warranted because of the rarity of hamartomas and because no other case at such an early age has been found in the literature. The present case is the eighth in the American literature and the fourteenth reported throughout the world.

A hamartoma is a nodular-like area, caused by a dysplasia of local tissue development. As originally described by Albrecht,[1] a hamartoma differs from a neoplasm in that, instead of arising from a single-cell type, it is a disturbance on an organoid level, consisting of an overdevelopment of the normal tissue elements of a given organ, and is usually benign in nature.

The typical lesion consists of a minute nodule, nonencapsulated, indistinct from the surrounding stromal tissue, formlessly arranged, and enclosing aberrant tubules. A wide variety of unrelated lesions has been included under the term hamartoma, resulting in ill-defined limits of classification and description.

At present the etiology of hamartomas is unknown, although hormonal imbalance and anomalous development have been implicated as important etiological factors. A definite hereditary tendency has been noted.

### CASE REPORT

Case No. 517230.—C. H., a 3-month-old white female infant, had, for one month prior to admission to Presbyterian Hospital of Chicago, recurrent bouts of chills, fever, and convulsions. The mother had noted a small mass in the lower abdomen on several occasions. A diagnosis of congenital heart disease and a kidney infection, possibly associated with a renal tumor, had been made when she had been hospitalized elsewhere.

Examination revealed an irritable infant with a rectal temperature of 103° F., whose irritation was increased on palpation of the left kidney area. No cardiac abnormalities were identified. An ill-defined mass was felt in the suprapubic area. The urinalysis was normal except for the presence of many white blood cells. A mild anemia and leukocytosis were present.

An intravenous pyelogram was attempted but was unsuccessful. The nonprotein nitrogen of the blood was reported as 63 mg. per 100 c.c. of blood. Cystography revealed a left ureterovesical reflux, a hydroureter, and a hydronephrosis. The bladder appeared trabeculated, and a possible diverticulum near the right ureteral orifice was noted. A diagnosis of bladder neck obstruction was made.

Insertion of an indwelling urethral catheter drained a very cloudy urine. *Streptococcus hemolyticus* was cul-

From the Department of Urology, Presbyterian Hospital of Chicago.

tured from the urine which was most sensitive to Chloromycetin. A combination of continuous catheter drainage plus Chloromycetin over a period of seven days caused the temperature and urine to revert to normal, while the nonprotein nitrogen blood level fell to 47 mg. per 100 c.c. of blood.

Eleven days after admission the patient had a cystoscopic examination which revealed a left ureterocele and a generalized subacute cystitis. A second intravenous pyelogram was performed three days later, disclosing a normal right kidney and ureter. The catheter was reinserted, resulting in an amelioration of the symptoms. A week later the catheter was removed without any untoward effects.

A diagnosis of double kidney with a double pelvis, tumor of the kidney, mixed congenital (hamartoma), hydronephrosis congenital, and pyelonephritis was reported by the pathologist, Dr. George Hass.

The specimen consisted of a 5 by 2 cm., 30-gram kidney with fetal lobulations, extending from which were two patent ureters, widening

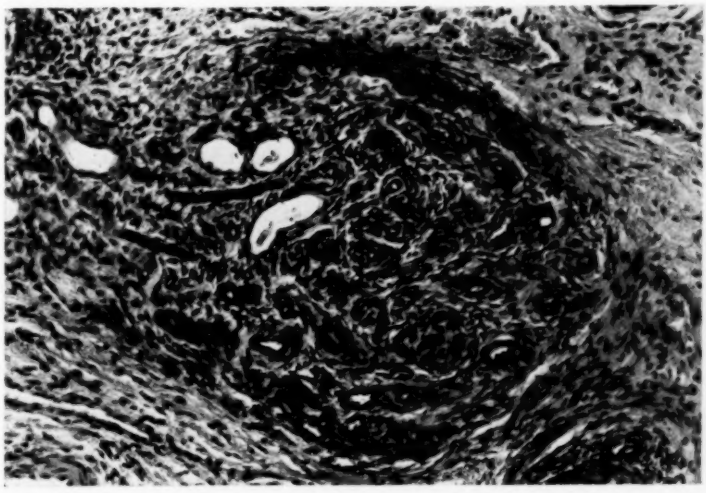

Fig. 1.—Photomicrograph (low power) revealing a nest of aberrant cysts, lined by flattened epithelium, and surrounded by a rich muscle and fibrous tissue stroma. Vascular component is prominent.

The following day a left nephroureterectomy was performed, with removal of a dilated kidney and pelvis attached to two ureters, each approximately the size of a small bowel.

The postoperative course was uneventful until the fourth day, when, after the removal of the urethral catheter, the patient had a rise in temperature followed by an attack of hematuria. Urine was observed to drain from the inferior aspect of the incision, presumably due to the ligature becoming loosened on the short segment of the left ureteral stump. out in the distal half. A cystic structure in the kidney parenchyma was observed on multiple sectioning.

Serial sections were taken for microscopic study. A section through the cyst revealed an empty lumen covered by simple cuboidal epithelium and surrounded by a wide fibrotic tissue zone. Toward the periphery were several small nests of tubular structures lined by columnar cells with a heavy zone of smooth muscle. Other structures were more cystic in character and were lined by a flattened epithelium. At one point

an oval-shaped mass of hyaline cartilage was present. These were small abortive glomeruli in various stages of formation. Venule tubules were also present. These ectopic nodules were fairly vascular and had a richly cellular stroma. In general there was more fibrous tissue present in the section than would ordinarily be expected, and the tubular development was moderately retarded. Here and there were local lymphocytic accumulations throughout the stroma and in the thick capsule (Fig. 1).

The pelvis appeared to have a thick fibrous wall with a large number of lymphocytes and monocytes plus sporadic erosions of the pelvic mucosa.

In another section there were many portions of the renal parenchyma showing extensive widespread fibrosis and infiltrations, plus many lymphocytic cells.

Sections through the ureters revealed a somewhat edematous and widened stroma containing lymphocytic accumulations and a thickened muscularis layer.

## DISCUSSION

The kidney cortex is involved in over 80 per cent of the cases of renal hamartomas. In the majority of cases the lesions are benign in nature and relatively asymptomatic due to their small size, with a tendency to remain latent. Occasionally, renal hamartomas progressively increase in size and, especially if bilateral, may reach such proportions as to cause renal parencyhma compression, producing a state of insufficiency.

A hamartoma may exist as an isolated entity or as part of the tuberous sclerosis complex, a chronic disease affecting ectoderm and mesoderm cell layers, predominately involving the nervous system, heart, kidneys, and skin. Approximately 50 to 80 per cent of the lesions are associated with the tuberous sclerosis complex.

On gross examination the individual nodule, only a few millimeters in diameter, is grayish-yellow to white in color, of variable consistency, usually nonencapsulated, and poorly differentiated from the surrounding tissue. Some of the nodules project from the cut surface.

Histologically one notes many anomalous cystic tubules with thickened stroma, lined with simple flattened cuboidal epithelium, and containing a clear fluid. The stroma consists of smooth muscle fibers intermingled with fibrous tissue. There is a remarkable paucity of striated muscle and elastic fibrous tissue. The vascular component is quite conspicuous, usually being well developed, and may even predominate in a given nodule, producing a distinctly angiomatous character.

In some areas the entire tissue is composed of ill-defined bundles of vasoformative cells without definite order except for circular alignment into groups of serpentine, thick-walled, small-lumened, medium-sized vessels. Necrosis, inflammatory reaction, or cellular infiltrations are rarely present.

A neoplasm is often suggested by the architecture of the lesion and the frequent appearance of atypical cells. However, when the organoid morphology, latent growth tendency, and the underlying nature are considered, a diagnosis of hamartoma is made.

The prognosis is the best in the isolated benign lesion and poorest when associated with the tuberous sclerosis complex. Death results at an early age in the latter case from the

cerebral lesions themselves, a subsequent development of status epilepticus, renal insufficiency, or a progressively developing state. Only three authenticated cases of malignant degeneration with metastasis have been reported.

The treatment, as might be expected, is not standardized. A small latent lesion would require no specific treatment. An asymptomatic large nodule is best treated conservatively or at most with irradiation, hamartomas being radiosensitive. Lesions producing symptoms necessitate surgical extirpation.

## CONCLUSIONS

1. A case report of a 3-month-old female infant with an isolated renal hamartoma is presented, the eighth ante-mortem case in the American literature and the thirteenth reported throughout the world.

2. The lesion was an incidental finding in a congenitally abnormal, poorly functioning, infected kidney.

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# SALMONELLA MENINGITIS

## Recovery From Meningitis Due to Salmonella of an Unknown Type

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Chicago, Ill.

Beene and associates[1] in 1951 reported a case of *Salmonella montevideo* in an infant and included a summary on eleven salmonella types described in eighty separate reports. They also reported in their review seventy-two fatalities of eighty-seven reported cases, a death rate of 82.7 per cent. Henderson[2] in 1948 reported a death rate of 87.5 per cent in a series of 147 patients.

It is the purpose of this paper to report a case of recovery from salmonella meningitis, which in the light of the above-mentioned percentages is encouraging.

### CASE REPORT

L. H., a 21-month-old Negro female infant, was admitted to the surgical department of the hospital after having fallen seven feet from a stairway on Aug. 10, 1953. She struck her head as a result of the fall and remained unconscious for a few minutes afterward. On her way to the hospital, and twenty minutes after the fall, the patient was noted to have had a momentary right-sided tetanic convulsion. She arrived at the hospital and was admitted approximately forty-five minutes after the fall.

The past history was not contributory. Five other siblings as well as the parents were in good health and had experienced no diarrhea or gastric upset. Feeding, developmental, and immunization history was adequate. The systemic review was negative.

*Physical Examination.*—Examination revealed a well-developed Negro female infant who was conscious, irritable, and alert. The nose bled slightly. There was a swelling on the left side of the head above the ear which was diffuse in nature but without evidence of a depressed fracture of the skull. Pupils were round and equal and reacted to light. There was no papilledema. Nuchal rigidity was absent. The chest examination was negative as was that of the abdomen, extremities, genitals, and back. Kernig's and Brudzinski's signs were absent. All reflexes were physiologic. The skull roentgenograms were negative.

*Clinical Course.*—For the next three days the child did well and showed no evidence of a neurological disturbance. On the fourth hospital day, the infant became lethargic and semicomatose and responded only to painful stimuli. The right arm and leg began to twitch during examination. A left horizontal nystagmus was noted. The convulsive seizure lasted about two minutes, and examination afterward revealed increased deep tendon reflexes on the right and a right facial paresis. No papilledema was present. The temperature spiked to 103.6° F. A lumbar puncture was performed revealing an opening pressure of 180 mm., closing pressure of 110 mm., glucose 30 mg. per 100 c.c., protein 128 mg. per 100 c.c., 1,250 cells predominantly polymorphonuclear, and 550 red blood cells. It was felt at this time that the patient had a subdural hematoma, complicated by meningitis. Penicillin, 600,000 units every twenty-four hours,

From the service of Dr. A. Rosenblum, Cook County Hospital, Department of Pediatrics.

and streptomycin, intramuscularly ½ Gm. every twenty-four hours, were started.

On the fifth hospital day nuchal rigidity was marked, abdominal reflexes were absent, and a positive Babinski reflex developed on the right. No further convulsions were experienced. Motor function was good. The child was alert and swallowing without difficulty. Neurological examination was otherwise much the same as the previous day. The temperature was 101.0° F., but it never reached normal levels. Chest and eye, ear, nose, and throat examinations were negative. Clinically the infant appeared much improved.

Culture of the previous cerebrospinal fluid grew a salmonella group D organism* sensitive to Aureomycin, Chloromycetin, and Terramycin.

On the sixth hospital day, the patient became semistuporous, and the temperature rose to 103° F. She was transferred to a medical ward where 250 mg. of Terramycin in 200 c.c. of 5 per cent dextrose in water was started intravenously and 100 mg. every six hours intravenously. Fluid therapy was instituted.

During the next three days the temperature dropped to normal and the patient became more interested in her surroundings and was able to take oral nutrition well. She was then placed on oral Terramycin. After seven days of oral medication, diarrhea developed and medication was stopped. During the next twenty-four hours the temperature rose to 101° F. The patient was very irritable, assumed a froglike position, and began vomiting feedings. Intravenous therapy was started again along with Terramycin.

On the twenty-fourth hospital day, lumbar puncture revealed a salmonella organism on culture by the New York Salmonella Typing Center and the Illinois State Health Laboratory. The specific type again could not be determined owing to lack of flagellar motility.

The clinical picture was poor through the thirty-fourth hospital day. A four-day course of intravenous Aureomycin was tried. The temperature rose to 103.8° F. on the third day of this therapy, and hence this antibiotic was stopped. Whole blood 150 c.c. transfusions were given. The infant began to take oral fluids and seemed somewhat improved as a result of the whole blood. Chloromycetin was started per os, 250 mg. initially and 200 mg. every six hours. The temperature was normal on the second day of Chloromycetin therapy but rose to 101° F. on the fourth day. The dosage was increased to 250 mg. every six hours. On the fifth day of this therapy the infant was alert, sitting up and eating solids such as mashed bananas; neurological signs persisted, and the patient was still very irritable.

After a week of Chloromycetin therapy, lumbar puncture revealed a glucose of 35 mg. per 100 c.c., protein of 280 mg. per 100 c.c., and 51 white blood cells (predominantly polymorphoneuclear cells), and many crenated red blood cells. An unsuccessful tap had been performed previously. Chloromycetin was given for ten days. The temperature was not elevated during the last six days of therapy. Flaccidity and nuchal rigidity began to decrease. Deep tendon reflexes were less hyperactive. The child appeared to have a stare, but funduscopic examination revealed no signs of increased pressure intracranially.

Head circumference was 18 inches and the chest circumference was 18½ inches. Eating became less of a problem, and fluid therapy was stopped. The patient recovered gradually. At the end of a three-month period she did not exhibit any neurological sequelae. Her appetite was good. Weight was 22½ pounds for a 24-month-old infant. Her attitude was alert, and she played actively. Three-word sentences were spoken readily. The appearance of a hydrocephalic

*New York Salmonella Typing Center and the Illinois State Health Laboratory confirmed the presence of a salmonella organism but were unable to type it.

"stare" was no longer suggestible. Lumbar puncture prior to discharge revealed a free flow of fluid, a glucose of 64 mg. per 100 c.c., a negative Pandy's, smear test, and culture, chlorides 113 meq. per liter, and protein 26 mg. per 100 c.c.

Summary of laboratory studies was as follows: Urinalysis and urine cultures were negative through the hospital course. Blood count on admission was 3.65 million red blood cells per cubic centimeter, 54 per cent hemoglobin, 19,400 white blood cells with a normal differential. Prior to discharge the blood count was red blood cells 3.71 million, hemoglobin 65, white blood cells 10,200, 46 polymorphonuclear cells, 8 bands, 3 eosinophils, 31 lymphocytes, and 12 monocytes. Three blood cultures were negative. Blood agglutinations were negative for salmonella on Sept. 14, 1953, but were 1:160 for typhoid H and 1:80 for typhoid O. Repeat agglutinations were positive for typhoid H and O in 1:1,280 and 1:640 dilutions, respectively, on Nov. 6, 1953. Stool examination for ova and parasites was negative as were stool cultures. Chest x-ray and Mantoux studies were negative. Cerebrospinal fluid examinations have been given previously.

Stool examinations and blood agglutinations of the parents and five siblings were negative.

## COMMENT

It is interesting to note that with all of the various antibiotics at our disposal a specific antibiotic for the salmonella has not come to pass. Moreover, the literature suggests the use of multiple antibiotic therapy as a method of attack on salmonella meningitis. Stein and Evans[3] report the recovery of two infants aged 19 days and 3 months with the use of multiple antibiotic therapy. Chloromycetin was used longer in the therapy regimen, a total of sixteen days in the 19-day-old infant, than any of the other antibiotics, which included Aureomycin, sulfadiazine, streptomycin, and penicillin. In the 3-month-old infant Chloromycetin was used for over three weeks and streptomycin, Gantrisin, and Terramycin for lesser periods of time. Salmonella type bredeney was the organism cultured in both cases. Kanton[4] reported a case of salmonella bredeney meningitis in which the patient recovered under multiple antibiotic therapy. Chloromycetin was thought to be an effective agent against salmonella, and this antibiotic was continued in use for seventeen days until the spinal fluid was clear. Chigier,[5] using several antibiotics, principally Chloromycetin, reported one death in a 4-month-old infant in whom *Salmonella enteritidis* was cultured and a recovery from the effects of *Salmonella typhosa* in a 3-month-old infant after penicillin and Chloromycetin were used for twenty-one days and sulfadiazine for four days in the latter case.

In the case presently reported various antibiotics were given throughout the treatment course. Not until Chloromycetin therapy was initiated, however, was there a negative culture of the spinal fluid. With the onset of whole blood therapy and Chloromycetin a definite improvement was noted clinically. In the cases noted, multiple antibiotics were used. Chloromycetin was used in all therapy regimens and, though various antibiotics were taken out of the therapy, Chloromycetin was relied upon until definite evidence of recovery was assured. The tendency then in these cases where patients have recovered, save that of Chigier, is to use numerous antibiotics

and to rely on Chloromycetin, which has a good Gram-negative spectrum, for the salmonella group infections.

## SUMMARY

A case of salmonella meningitis has been presented in which the patient survived with the use, principally, of whole blood and multiple antibiotics. The main therapeutic effect was due to Chloromycetin. Several other cases of recovery with multiple antibiotic therapy and one fatal case are noted.

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# Medical Progress

## ANOMALIES OF INTESTINAL ROTATION AND MESENTERIC FIXATION

### Review of the Literature With Report of Nine Cases

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#### INTRODUCTION

ANOMALIES of intestinal rotation and mesenteric fixation present varied and interesting problems in diagnosis and management to both pediatrician and surgeon. They are of interest because patients with such anomalies may present with symptoms and signs of intestinal obstruction, strangulation, or complaints suggesting an underlying functional or psychogenic disorder, and a small proportion may present a picture suggesting celiac syndrome. These anomalies must also be kept in mind by the clinician in evaluating abdominal pain and its distribution. That the appendix does not always lie in the right lower quadrant is unrecognized by many. Anomalous intestinal rotation may challenge the surgeon who opens the abdomen only to find anatomic relations are not as anticipated, and this may be especially troublesome when the incision is not of a type amenable to easy extension and adequate exposure. Finally, there exists a substantial group of patients in whom these anomalies are asymptomatic and are discovered only when they are studied radiographically with gastrointestinal series or barium enema for other unrelated complaints. This paper will review the literature on these anomalies and report nine cases in the pediatric age group treated at the Raymond Blank Memorial Hospital for Children from 1947 to 1953.

From the Raymond Blank Memorial Hospital for Children.

#### HISTORICAL DATA

Conditions resulting from anomalous intestinal rotation and mesenteric fixation have been known since at least 1786 when Neubauer recorded the first case of paraduodenal hernia.[1] In the last century Reid, in 1836, and Simpson, in 1839, described rotational anomalies.[2] From 1865 to 1901 isolated cases of volvulus involving small bowel, cecum, and transverse colon, invariably with fatal issue, were reported, and in 1903 a series of five such cases was reported, also with fatal results. In 1904 Mohring reported the first successful surgical treatment of midgut volvulus in a 72-year-old woman who had an uneventful recovery.[3] During the first two decades of this century isolated cases were reported from the dissecting room[4] and operating room where these anomalies were usually coincidental findings.[5] During this period some cases were reported that presented findings strongly suggestive of anomalous intestinal rotation or mesenteric fixation but which seem to

have gone unrecognized owing to inadequate exploration or radiologic study.[6] In 1898, some years after Meckel's description of the egress of the midgut loop into the umbilical cord during the fifth week of gestation, Mall[7] described its return to the abdominal cavity. In 1915 Frazer and Robbins[8] discussed the factors causing the rotation of the intestine. However, it was not until 1923 that anomalies of intestinal rotation and mesenteric fixation were thoroughly worked out and their common pathogenesis described by Dott[9] in his masterful article. It is on Dott's work that most subsequent discussions of these anomalies, their pathogenesis and classification, have been based.

### INCIDENCE

Dott[9] was able to find records of abnormalities in midgut rotation and mesenteric fixation in forty-five instances with only a brief review of the literature to 1923. However, he found there were only rare instances of errors in disposition of the foregut (that part proximal to the biliary ampulla) or the hindgut (that part of the bowel distal to the left end of the transverse colon). Waugh[10] reviewed the findings at operation in 180 patients who had varying degrees of failure of rotation of the cecum in the normal clockwise direction with subsequent abnormal fixation of the mesentery posteriorly and found that 77 per cent had a right-sided ascending colon with a complete primitive mesentery from the hepatic flexure to the cecum. He noted that abnormalities of colon attachment may vary from instances of complete nonrotation to those in which all but a vestige of primitive mesentery has disappeared. In addition, he quoted a study of several hundred routine autopsies at the Great Ormond Street Hospital for Children in which it was found that 20 per cent showed some persistence of the primitive dorsal mesentery.

Distribution by age and sex of thirty-three cases of anomalies of intestinal rotation and mesenteric fixation reviewed by Haymond and Dragstedt[2] is given in Table I.

TABLE I. ANOMALIES OF INTESTINAL ROTATION AND MESENTERIC FIXATION

| AGE (YEARS) | NUMBER | MALES | FEMALES | SEX NOT GIVEN |
|---|---|---|---|---|
| Under 10 | 11 | 3 | 8 | 2 |
| 10 to 20 | 3 | 1 | 1 | |
| 20 to 30 | 6 | 3 | 3 | 1 |
| 30 to 40 | 4 | 2 | 1 | |
| Over 40 | 4 | 2 | 2 | |
| Not given | 5 | 3 | 1 | |
| Total | 33 | 14 | 16 | 3 |

Reviews by other writers are tabulated in Table II. Of especial interest is the long duration of symptoms experienced by some patients and the onset of symptoms relatively late in life.

More recently Brown and Ross[13] reported that 10 per cent of all patients operated upon for intestinal obstruction at a Naval Hospital had some gross error of intestinal rotation of mesenteric fixation. Unfortunately, they did not give the total number of cases involved. Finally, Gross,[14] in his text of 1953, gave figures on the types of associated congenital anomalies in 156 cases of malrotation treated by the Ladd procedure (Table III).

It is impossible from the literature to make any accurate estimate of the

incidence of these anomalies in reference to the population as a whole. However, from the data tabulated here, it is apparent that: (1) most anomalies of the disposition of the gut involve the midgut loop and its derivatives, (2) minor aberrations in mesenteric fixation are common, (3) these anomalies may often remain asymptomatic for a lifetime or occasionally cause only trivial symptoms, (4) obstructive symptoms are much more likely to occur in infancy and childhood, and (5) there appears to be virtually equal sex distribution of such anomalies.

TABLE II. ANOMALIES OF INTESTINAL ROTATION AND MESENTERIC FIXATION RECORDED IN THE LITERATURE

| SOURCE | NUMBER | TYPE OF ANOMALY | MALES | FEMALES | AGE RANGE | MAXIMUM DURATION OF SYMPTOMS | HOW DIAGNOSED |
|---|---|---|---|---|---|---|---|
| Truesdale[11] | 11 | Retroposition of transverse colon | 5 | 6 | 7 da. to 68 yr. | 19 yr. | 6 at operation<br>5 at autopsy |
| Gardner and Hart[12] | 88 | Midgut volvulus | 54 | 34 | Newborn to 50 yr. | 20 yr. | 56 at operation<br>32 at autopsy |
| Gardner and Hart[12] | 4 | Anomalous duodenal fixation | 0 | 4 | Newborn to 57 yr. | 5 yr. | 3 at operation<br>1 at autopsy |

TABLE III. ASSOCIATED CONGENITAL ANOMALIES IN 156 CASES OF MALROTATION TREATED BY THE LADD PROCEDURE

| ASSOCIATED ANOMALY | INCIDENCE |
|---|---|
| Duodenal stenosis or atresia | 11 |
| Pyloric stenosis | 4 |
| Biliary obstruction | 3 |
| Congenital heart disease | 3 |
| Esophageal atresia | 3 |
| Omphalocele | 2 |
| Other anomalies | 5 |
| Total | 31 |

## EMBRYOLOGY

Because of the rapid growth of the midgut segment of the embryonic gut, a large loop is formed, convex anteriorly, which herniates into the umbilical cord during the fifth week of gestation. It carries with it the mesentery through which passes its blood supply, the superior mesenteric artery. For descriptive purposes, the proximal portion of the midgut loop is referred to as "prearterial" while the distal part is termed "postarterial." During the fifth week of gestation the differentiation of cecum and appendix becomes apparent and constitutes quite a swelling on the postarterial segment. Dott has described the return of the midgut loop from the umbilical cord to the abdomen in three stages, and this plan will be summarized before considering various abnormalities which may occur.

*First Stage of Rotation.*—The first stage begins when the midgut loop lies within the umbilical cord. At this time the prearterial and postarterial gut segments are in close approximation within the narrow confines of the umbilical orifice. Soon, growth of the right lobe of the liver forces the prearterial segment downward and to the right within the umbilical orifice, while the postarterial

segment is forced upward and to the left, completing the first stage of rotation.

*Second Stage of Rotation.*—The second stage begins about the tenth week of gestation with the prearterial segment returning first through the umbilical orifice to the now much larger fetal abdominal cavity, the small bowel coming to lie posterior to the superior mesenteric artery. It is followed by the postarterial segment, the distal colon leading, until at last the cecum is reduced. The cecum now lies free in the abdominal cavity, anterior to the small intestine. The colon, tending to straighten out, carries the cecum upward and to the right, while the colon comes to lie across the pedicle of the mesenteric mass at the origin of the superior mesenteric artery. Growth of the ascending colon causes the cecum to descend toward the right iliac fossa, and the second stage of rotation is complete.

*Third Stage of Rotation.*—The third stage consists of the further descent of the cecum and the fixation of certain parts of the intestine to the posterior parietal peritoneum. The cecum reaches its final location by the fifth month of gestation. The third and fourth parts of the duodenum, having come to lie posterior to the superior mesenteric artery, become fixed there by fusion of its mesentery with the posterior parietal peritoneum posteriorly and the mesenteric pedicle anteriorly. Thus the duodenojejunal flexure is established. The postarterial mesentery of the cecum, ascending colon, and hepatic flexure becomes obliterated by fusion with the posterior parietal peritoneum. The postarterial mesentery of the transverse colon, however, persists as mesocolon. To the left of a line of adhesion along the superior mesenteric artery and its branches, the prearterial mesentery remains free as the small bowel mesentery with its wide, obliquely placed root. Dott[9] stated, "The practical importance of the third stage lies less in the minor degree of rotation it completes, than in the fixation of the parts in such a way that displacement, and especially torsion and volvulus, are rendered impossible."

## ANOMALIES

Anomalies of intestinal rotation and mesenteric fixation may be classified according to the stage of embryonic development in which error occurred. This approach is logical, it provides an explanation of how and when the developmental error occurred, and requires the clinician to be mindful of the full variety of embryonic aberrations. One can only speculate as to why these errors occur. In classifying such an anomaly, the following data are desirable: (1) on which side of the vertebral column the duodenojejunal junction lies, (2) the anterior-posterior relations of the superior mesenteric artery and the third and fourth parts of the duodenum, (3) the anterior-posterior relations of the duodenum and colon, (4) the location of the cecum, (5) the relationships of the inferior mesenteric artery, and (6) any abnormal mesenteric bands which exist. Unless these questions can be answered, a given anomaly is not well understood, and these data are not included in many reports, which has detracted much from their value in the literature.

TABLE IV. CLASSIFICATION OF ANOMALIES OF INTESTINAL ROTATION AND MESENTERIC FIXATION

| |
|---|
| I. First stage of rotation |
| A. Extroversion of the cloaca |
| II. Second stage of rotation |
| A. 1. Malrotation |
| 2. Malrotation associated with omphalocele |
| B. 1. Reversed rotation, retroposition of the transverse colon |
| 2. Reversed rotation, paraduodenal hernia |
| C. Duodenum inversum |
| III. Third stage of rotation |
| A. Incomplete fixation of the colon |
| B. Anomalous fixation of the duodenum |

I. *Anomalies of the First Stage.*—Failure of rotation in the first stage occurs only in association with extroversion of the cloaca, a rare developmental error. In this condition, intestine, ureters, and genital ducts all open on the extroverted surface. The ileum usually is the terminal part of the functional bowel present, while the colon is represented only by ectopic bits of tissue scattered over the extroverted cloacal surface. This anomaly is thought to arise because of early rupture of the cloacal membrane with exposure of the undifferentiated cloaca and the enteric and ureteric orifices emptying into its dorsal aspect.[9, 15] It is also felt that a basic embryologic defect in this deformity is a local failure of mesodermal development which is consistent with the known frequency of agenesis of the os pubis and also with the fact that defects in the lower spine are very often also seen in infants with this defect.[36, 39]

II. *Anomalies of the Second Stage.*—Errors occurring in this stage of intestinal rotation are the ones which most often become surgical problems. Indeed, the variety of abnormalities which may be found within the abdomen incident to these errors is almost without limit. Broadly speaking, they may be divided into two general types: "malrotation," i.e., situations where the cecum has failed to rotate at all or has rotated incompletely through its normal 270 degrees counterclockwise arc, and "reversed rotation" where the cecum rotates in an abnormal clockwise direction through an arc of as much as 90 degrees, often coming to lie in the right lower quadrant. Malrotation may be subdivided into uncomplicated malrotation and that associated with omphalocele. Reversed rotation may result in the cecum coming to lie in the right lower quadrant with the transverse colon lying in back or in front of the duodenum, the latter presenting some very interesting problems. Finally, there may be seen as an anomaly of the second stage, "duodenum inversum" in which the duodenum follows an anomalous course.

A.1. *Malrotation.*—This is a condition well described in Gross's recent textbook and will therefore be only briefly reviewed here. It arises owing to failure, of variable degree, of the cecum to rotate through its normal 270 degree arc of counterclockwise rotation. It may, therefore, be found just behind and above the umbilicus, in the right upper quadrant, or at any level in the right side of the abdomen. Since abnormal rotation involves abnormal fixation, two additional abnormalities of mesenteric fixation are likely. They are obstructive duodenocolic bands,[16] which may also involve the gall bladder,[17] and rudimentary posterior fixation of the small bowel

mesentery. Abnormal mesenteric bands may lead to obstruction of the second or third parts of the duodenum, the Ladd-Waugh syndrome, while the rudimentary small bowel mesentery may produce volvulus of the small bowel because of its narrow base. In a substantial proportion of patients both conditions obtain concurrently.[18]

In the literature are reports of a number of cases of malrotation complicated by volvulus involving the entire midgut loop from the distal part of the duodenum to the splenic flexure. This situation arises where the midgut loop, from duodenum to mid-transverse colon, hangs on a rudimentary mesentery, of variable length, with poor fixation posteriorly. Usually such patients have a duodenum situated entirely on the right, lateral to the superior mesenteric artery. Volvulus of the midgut segment may produce duodenal obstruction due to kinking of the duodenojejunal junction, or embarrassment of the circulation through the superior mesenteric artery.[9, 19-23]

A.2. *Malrotation Associated With Omphalocele.*—In his article of 1923, Dott[9] reported two cases of omphalocele with associated malrotation, and this seems to be the earliest instance in which the close embryologic relationship of these two congenital abnormalities was clearly recognized. Gross[14] reported that in a series of eighty-eight patients with omphalocele treated at the Boston Children's Hospital, 28 per cent showed malrotation which had to be treated at the time of omphalocele repair or subsequent thereto. He stressed that the clinical importance of this relationship lies in the fact that vomiting after omphalocele repair is sometimes a clear sign of intestinal obstruction for which another operation may be urgently needed. If, as Gross suggested, the basic reason for omphalocele development is failure of the abdominal parietes to grow adequately during the period when the midgut loop normally lies in the umbilical cord, it is difficult to understand why omphalocele is not always associated with malrotation. The answer may lie in the fact that these children have abnormally large umbilical orifices which may permit an irregular return of the large bowel to a normal position in the abdominal cavity while the small bowel remains in the sac.

B.1. *Reversed Rotation, Retroposition of the Transverse Colon.*—In this uncommon situation, the cecum and colon must have returned first to the abdominal cavity from the umbilical cord. The large bowel then undergoes 90 degrees counterclockwise rotation so that the cecum lies in the right lower quadrant, but the transverse colon comes to lie posterior to the duodenum and superior mesenteric artery. The small bowel is reduced last and usually its mesentery undergoes fixation along a normal, broad, obliquely situated base. This results then in the right transverse colon passing through a tunnel of small bowel mesentery at the level of the duodenum. Usually the posterior fixation of the cecum and ascending colon is not complete, and they are found to have a free mesentery.[9]

One of the earliest reports of this unusual anomaly was of a case in which a reduplication of the upper jejunum appears to have been a mechanical deterrent to the return of the prearterial segment to the abdominal

cavity before the postarterial segment.[24] Usually, however, the basic reason for the anomaly is obscure. Most of the reported cases have come to operation because of obstruction of the transverse colon at the point where it passes through the mesentery of the small bowel.[11, 25-27] Perforation of the transverse colon proximal to the obstructing mesentery has been reported.[28] Asymptomatic cases where the anomaly has been a coincidental finding at operation have also been reported.[11] Silverman and Caffey[29] feel the condition can be recognized radiologically by demonstrating that the transverse colon passes posterior to the duodenum.

B.2. *Reversed Rotation, Paraduodenal Hernia.*—As noted previously, these interesting anomalies were the first type of anomalous intestinal rotation and mesenteric fixation described; but about one hundred and thirty years elapsed before their pathogenesis began to be understood, and even then the literature was not characterized by any great degree of lucidity. Until the early 1920's it was generally accepted that these anomalies were herniations of small bowel into the various peritoneal folds or "fossae" about the duodenojejunal junction, following the dictum of Moynihan.[37] In 1923, Andrews[30] reviewed the literature and found the situation "absurd and grotesque" because: (1) differential pressure at the site of hernia is lacking, (2) there are hundreds of similar folds and fossae in the peritoneum where herniae never occur, (3) the degree of hernia is usually total or subtotal, (4) they have been reported in the newborn infant, (5) the content of the hernia is never anything but small bowel, and (6) there is an almost universal growing together of the contents of the sac, but the adhesions are loose and do not give the appearance of inflammatory adhesions. He defined a right paraduodenal hernia as one in which the sac lies to the right of the duodenum with the superior mesenteric artery or its continuation, the ileocolic artery, lying in the free edge of the fold forming the sac's anterior wall. A left paraduodenal hernia lies to the left of the duodenum with the inferior mesenteric artery and vein in the free edge of the sac which lies between these two vessels. Andrews suggested that these so-called paraduodenal hernias were, in fact, anomalies of intestinal rotation and presented splendid diagrams to prove his point which are reproduced in part in Fig. 1. He felt these anomalies arose because the cecum and colon, during the second stage of intestinal rotation, rotated in a 90 degree clockwise direction and that, in the process, the small bowel became enveloped in either the mesentery of the ascending colon (right paraduodenal hernia) or the mesentery of the transverse and descending colon (left paraduodenal hernia). He noted there have also been reports of "mesocolic hernia" which he believed of similar origin, representing an intermediate form.

Later Haymond and Dragstedt[2] reported a case of paraduodenal hernia which they accepted as being an example of reversed rotation, an autopsy finding in an elderly carcinoma patient. Gardner and Hart[12] also accepted this etiology in their review of rotational anomalies. Callender and associates[31] in 1935 discussed the

mechanism of these anomalies and noted that the patient usually presented with intestinal obstruction a soft mass in the upper abdomen, and frequently gurgling was heard over the mass. McIntosh and Donovan,[32] in their review of rotational disturbances in children, stressed the fact that the differential diagnosis on such patients involved: functional vomiting, intestinal stenosis or atresia, diseases of the central nervous system with vomiting of central origin, and parenteral or enteric infections.

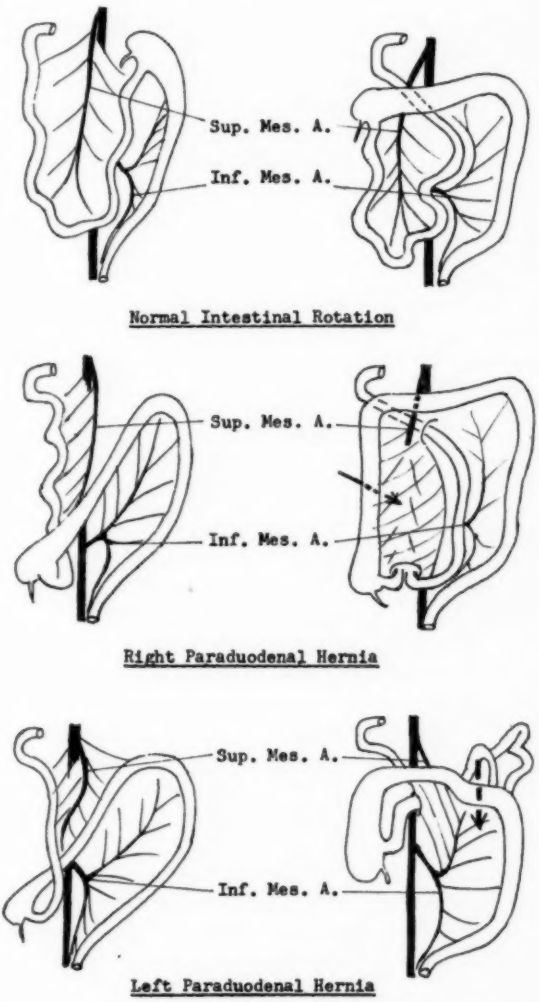



Fig. 1.—The pathogenesis of paraduodenal hernias. (After Andrews: Surg., Gynec. & Obst., 1923.)

In 1944, McCarty and Present[1] reported what they termed a mesenteric pouch hernia simulating a paraduodenal hernia. They discussed the literature on paraduodenal hernias and accepted the opinion that they were essentially rotational anomalies. However, since their case had an invagination of small bowel into the mesentery of the proximal jejunum, they felt its origin lay in an excessively long mesentery of the prearterial gut loop, which, by reason of its redundancy, made possible the herniation. They also emphasized the diagnostic importance of radiologic demonstration of the small bowel lying in a relatively fixed, well-circumscribed mass in the upper abdomen. More recently, other observers[13, 14, 33, 38] have written reports of these anomalies and accepted the concept that they are anomalies of intestinal rotation and mesenteric fixation.

C. *Duodenum Inversum.*—This asymptomatic anomaly of the duodenum was described in 1934 by Weinbren and McGregor,[34] who reported eleven cases discovered radiographically. Instead of following its usual course, as shown by barium studies, the first part of the duodenum was directed laterally, the second part downward and further laterally, the third part straight upward, and the fourth part obliquely upward and toward the midline. These observers discussed the literature and noted that duodenal fixation does not occur unless the dorsal mesentery disappears and that varying degrees of "duodenum mobile" exist which, in the extreme, permit the duodenum and pancreas to be lifted out of the abdomen and placed on the anterior abdominal wall. They feel that errors in the location of the right kidney, pancreas, and the transverse mesocolon are especially likely to be associated with malposition of the duodenum.

III. *Anomalies of the Third Stage.*—Waugh's[10] report of 180 cases of mobile ascending colon has already been mentioned, but it must be emphasized that 77 per cent had an ascending colon supported by a complete primitive dorsal mesentery. His observation that 20 per cent of a pediatric autopsy population showed some persistence of the dorsal mesentery is also important. Percentagewise, anomalies of the third stage of rotation are certainly the most common. Others have noted that early fixation of the ascending colon, or its failure to elongate, will result in a high or subhepatic cecum. Conversely, deficient fixation of the cecum or excessive elongation of the ascending colon will result in an overdescended cecum. Defective fixation of the postarterial mesentery produces varying degrees of "mobile proximal colon" from simply a mobile cecum to a "floating ileocolic segment" which may undergo volvulus and which, on occasion, has been found turned up underneath the spleen.[2, 9, 35]

Congenital obstructing peritoneal bands involving the proximal end of the midgut loop are also reported. Morton and Jones[23] reported eleven cases of high-lying intestinal obstruction in the newborn period. In four of their patients the sole cause of obstruction was the presence of several bands of peritoneum across the duodenum without associated rotational anomaly. In one of their patients a cystocolic ligament attached to the hepatic flexure produced torsion of

the second part of the duodenum. This latter is especially unusual since the incidence of cysticoduodenocolic folds is estimated at 25 per cent of the general population. They are presumed to be essentially normal products of mesenteric fixation and thought to be of pathologic interest only in the presence of inflammation in adjacent structures when they may rarely produce obstructive symptoms.[17] At one time such peritoneal bands were thought to represent fetal peritonitis, but this concept has fallen into disrepute.[5, 35]

*Factors Predisposing to Obstructive Symptoms.*—Two questions may be raised at this point: (1) Why does the newborn infant who has had an anomaly of rotation or fixation since about the twelfth week of fetal life suddenly develop obstruction and even strangulation in a matter of days post partum? (2) Why does the older person who has lived often without any symptoms at all suddenly develop acute symptoms? Answers must necessarily be speculative, but certain factors are implicated. The fetal bowel contains little material and peristaltic activity is at a low level, the nutrition being derived from the placenta. With birth the infant moves much more and his intestine assumes the burden of nutrition with increased peristalsis; and so the signs of intestinal obstruction appear. In the older patient, whose gastrointestinal tract has already served him more or less well, obstructive symptoms probably arise as a consequence of a sudden untoward movement of the body, exertion, or undue distention of a segment of bowel. Indeed, the onset of symptoms following unusual exertion has been reported.[9, 29]

## CASE REPORTS

CASE 1.—Baby boy H. (No. 226-438) was born Nov. 25, 1953, at Iowa Methodist Hospital, at which time he was noted to have multiple congenital anomalies, and was transferred immediately to Raymond Blank Memorial Hospital for Children. Examination revealed an infant who, though in no apparent distress, had a spina bifida 14 cm. long and flexion contractures of both lower extremities. There was a large omphalocele and extroverted cloaca onto the surface of which flowed both stool and urine. A bifid, rudimentary penis and scrotum were noted, no testicles being found in the latter. The anus was imperforate. Pediatric and surgical consultants felt the extent of the congenital anomalies contraindicated surgical intervention and that they were incompatible with life. General supportive treatment was given and on Dec. 7, 1953, the infant died after a progressively downhill course.

Post-mortem examination revealed that the liver, small bowel, and omphalocele sac were all bound together by rather dense adhesions. The stomach, duodenum, and small bowel had normal mesenteric attachment. There was no obstruction along the intestinal tract, which terminated where the lower ileum opened onto the extroverted cloacal surface and was the highest of three openings. Beneath this orifice another opening led into a blind pouch 10 cm. long, which curved over the pubis and into the left iliac fossa. The third and lowest opening lay just above the base of a bifid penis and was somewhat umbiliform in shape. Into this lowest opening the ureters emptied from either side. Joining the ureters just proximal to their openings were the spermatic ducts which led from testicles situated directly below and lateral to the kidneys.

Microscopic studies demonstrated a rather extensive bronchopneumonia in the peribronchial areas. There was an

acute pyelonephritis, and many pus cells were seen in the right epididymis. Examination of tissue taken from the blind pouch which opened posterior to the terminal ileum revealed it to consist of rectal mucosa with moderate thickening of the serosal surface. Ante-mortem changes in the extrophied surface precluded satisfactory microscopic study of this tissue.

*Comment.*—Anomalies of this type are very uncommon, and an illustration of a similar case but with a large umbilical hernia will be found in Campbell's *Clinical Pediatric Urology.*[36]

CASE 2.—E. D. T. (No. 40874), a 10-day-old male infant, was admitted to this hospital Jan. 13, 1947, with a complaint of having vomited all feedings since birth. Vomiting was bile-stained and projectile, and at one time peristaltic movements had been seen in the upper abdomen before admission. Physical examination revealed only dehydration of mild degree, though one observer thought he felt a tumor in the right upper quadrant. The day following admission, after the correction of the infant's fluid balance, upper gastrointestinal studies were made. These showed dilatation of the second part of the duodenum; the jejunum was found to turn back on itself just distal to the duodenojejunal junction, and 30 per cent retention of barium within the stomach was noted after three hours. Two weeks later, during which time the infant had done well on evaporated milk formula, a barium enema was performed which showed a constriction in the proximal transverse colon in the region of the junction of the second and third parts of the duodenum, with the cecum extending far to the left. Because the infant was symptom-free, operation was deferred, and on Feb. 15, 1947, the baby was discharged. Follow-up to the present (1954) finds the boy symptom-free and living an active life, never having had any symptoms referable to his known anomaly.

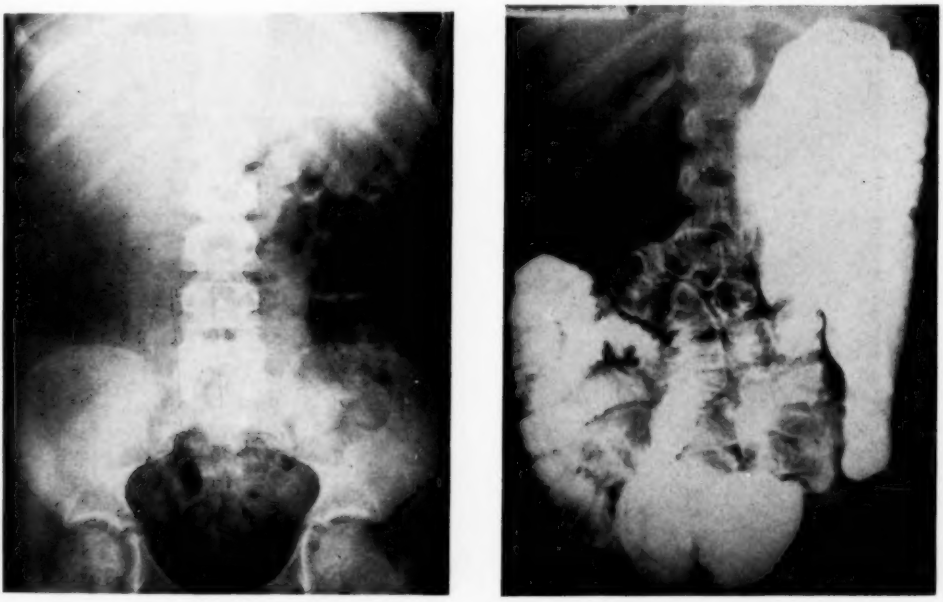
*Comment.*—This case is interesting in that it is an example of how asymptomatic anomalies of intestinal rotation and mesenteric fixation can be. It is unusual in that it is a rare example of a newborn infant who has had symptoms of duodenal obstruction which have subsided completely without recurrence.

CASE 3.—S. K. H. (No. 213-915), a 9-year-old girl, was admitted April 21, 1953, to this hospital for elective surgery for the relief of a known malrotation. For three years before admission she had had recurrent episodes of projectile vomiting of previously ingested food. These episodes had lasted as long as a week, and the accompanying abdominal pain had been of sufficient severity to cause the girl to lie with legs doubled up. Mucus had been noted in the stools for two months before admission. Radiologic studies at another hospital had established the existence of a malrotation of the cecum. Physical examination and laboratory work on admission were within normal limits. At operation, after a right rectus incision was made, the small bowel presented in the incision. The colon lay in the left side of the abdomen, and there was complete malrotation of the cecum with a rudimentary small bowel mesentery. An adhesive band was noted between the colon, the periduodenal area, and the ampulla of the gall bladder, beneath which the second and third parts of the duodenum protruded as a knuckle of bowel. It was felt at the time of operation that probably symptoms were due to intermittent duodenal obstruction together with occasional torsion of the small bowel on its pedicle. The duodenocystocolic band was divided. The mesenteric base was broadened by a row of sutures from the ligament of Treitz, obliquely downward, just to the right of the bifurcation of aorta. At the end of the operation the colon lay in the left side of the abdomen,

the small bowel just above it and to the left. Appendectomy was performed and the abdomen was closed. The postoperative course was uneventful.

*Comment.*—This case is an example of malrotation of the colon with duodenal obstruction and coexistence of a rudimentary small bowel mesentery.

stools had been passed followed by transitional stools. Physical examination revealed a slightly dehydrated infant with epigastric distention but was not otherwise remarkable. Flat film of the abdomen showed an absence of small bowel gas pattern. The day following admission a barium meal remained almost entirely within



*A.* *B.*

Fig. 2.—Case 3. *A*, Left-sided colon with small bowel gas pattern situated in the lower abdomen suggests rotational anomaly in the flat film. *B*, Barium enema substantiates this impression.

Sometimes it is found that the mesentery is not only rudimentary but also very short as well, and operative fixation is not possible as it embarrasses the circulation through the superior mesenteric artery. Subsequent volvulus is therefore possible.

Case 4.—D. C. (No. 48927), a 5-day-old male infant, was transferred from the newborn nursery June 23, 1947, with complaints of having vomited all feedings and of fecal vomiting between feedings. Several meconium

the stomach. Barium enema showed the cecum adjacent to the duodenal bulb. Because of pneumonia, the operation was deferred two days while vigorous treatment with antibiotics was given. At operation complete nonfixation of the small bowel mesentery with a 180 degree counterclockwise volvulus was found. The ascending and transverse colon lacked posterior fixation, and a duodenocolic band across the second part of the duodenum produced obstruction. The

duodenum descended without fixation through the mesentery over a loop of jejunum where the right small bowel hung on a pedicle. The surgeon stated, "I have never seen this type of anomaly and judge that it is a rudimentary effort of the duodenum toward fixation and the formation of a ligament of Treitz." The volvulus was reduced, the obstructing band divided, and the abdomen closed. The postoperative course was smooth.

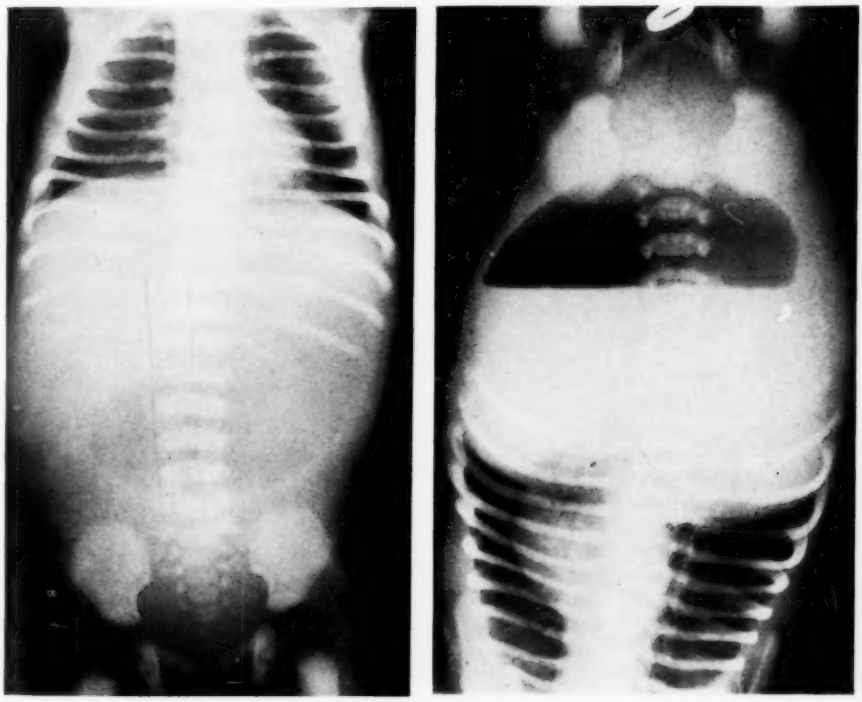
Fig. 3.—Case 4. The juxtaposition of cecum and duodenal bulb indicates the presence of an anomaly of rotation. The retention of barium in the stomach by a duodenal obstruction was also demonstrated.

*Comment.*—Deficient fixation of the entire midgut loop is seen in this case. The small bowel mesentery was rudimentary and underwent volvulus. There was lack of fixation of the duodenum, small bowel, and ascending and transverse colon with resultant abnormal fixation of duodenum and colon posteriorly which produced duodenal obstruction. The observation is well illustrated that where there is deficient mesenteric fixation, abnormal and often obstructive fixation is likely to occur.

CASE 5.—M. B. (No. 224-510), a 3-day-old female infant, was referred from another hospital Oct. 31, 1953, because she had vomited all feedings since birth. The infant took formula well and shortly thereafter vomited it, usually with some additional bile-colored fluid. She had passed currant jelly stools one hour after arriving home from the hospital where she was born. Physical examination revealed a slightly dehydrated infant with some abdominal distention and complete absence of peristaltic sounds. Flat film of the abdomen showed a grossly distended stomach one-half full of fluid and complete absence of small bowel gas pattern. Cut-down was performed, intravenous fluids were started, and operation was begun three hours after admission. At operation the stomach and duodenum were greatly dilated owing to volvulus of the small bowel, which lacked posterior fixation of its mesentery. The entire small bowel was markedly cyanotic. The duodenojejunal angle had undergone torsion with resultant complete obstruction in such a way that the portal vein passed over it, and the ileum became intraperitoneal through the mesentery of the terminal ileum. After reduction of the small bowel volvulus, circulation improved somewhat but seemed inadequate. The portal vein was compressed for a time, with the thought that perhaps it could be divided in this child; but the cyanosis of the small bowel became worse. The colon and terminal ileum, together with the duodenum, had an entirely adequate blood supply. The right colon and cecum, situated anterior to the duodenum, were rotated medially after a lateral peritoneal band was divided. The dilated retroperitoneal duodenum was outlined, and the mesentery of the terminal ileum and its contained portal vein were dissected from the

proximal duodenum so the portal vein could be placed in its normal location to the right of the jejunum. At the conclusion of the procedure the color of the small bowel was much improved, but there was still slight cyanosis. This patient recovered rather slowly postoperatively, but it was not until seven days later that oral fluids were begun. However, there were no complications and the follow-up for several months has been uneventful.

*Comment.*—This infant presented the most difficult problem at surgery of any in the present series. The difficulty arose from the lack of posterior fixation of the small bowel mesentery with resultant close approximation and torsion of the portal vein and small bowel at the root of the volvulus which made technically difficult reduction of the volvulus without impairment of the venous return from the bowel. It was not until the cecum and colon were mobilized to the left and the portal vein and duodenum placed in their proper relationship that anything approaching adequate portal return was obtained. At the time of closure there were some misgivings as to the degree of insult the bowel had sustained, and this is thought to have been a factor in the infant's rather slow recovery.



*A.* *B.*

Fig. 4.—Case 5. *A* and *B*, The grossly distended stomach and absence of small bowel gas pattern in the newborn infant is diagnostic of complete obstruction at the duodenum present since before birth.

CASE 6.—W. M. T. (No. 71246), a 1-day-old male infant, was transferred

to this hospital on Feb. 23, 1949, because he had been vomiting small amounts of fluids containing flecks of dark green material. Physical examination on admission revealed no significant abnormalities. Flat film of the abdomen showed less air in the small bowel than usual, which was thought to suggest a partial obstruction. There was also atelectasis of the left upper lobe. The following day the infant's condition became rapidly worse; the abdomen became distended and quiet. Respiration was grunting. He was felt to have an acute surgical abdomen with peritonitis and was prepared for surgery with transfusion, fluids, and oxygen. Dramatic improvement resulted. Flat film of the abdomen at this time showed a colonic gas pattern, mainly in the left upper quadrant, and a small amount of small bowel gas pattern in the left upper quadrant. The right side of the abdomen and the left lower quadrant appeared as a diffuse homogeneous density with obliteration of the peritoneal line on the left. At operation there was bloody fluid in the peritoneal cavity. The entire small bowel was gangrenous. A volvulus of two and one-half turns in a clockwise direction had occurred about a rudimentary mesentery the size of a pencil. There was nonrotation of the colon, and the cecum lay in the left upper quadrant. The abdomen was closed without operative intervention, and the patient died the following day. Post-mortem examination confirmed the operative findings.

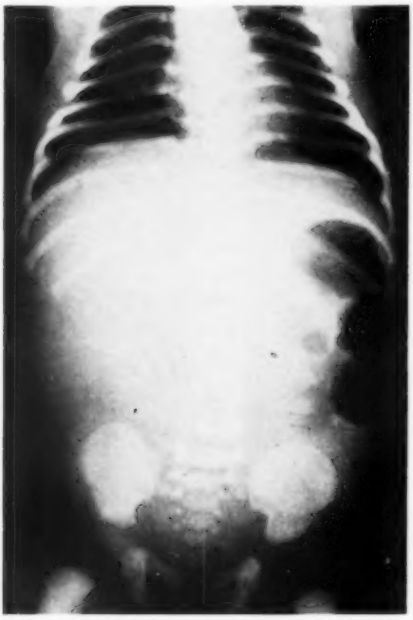


Fig. 5.—Case 6. Minimal small bowel and colon gas pattern in the left upper quadrant suggests intestinal obstruction with no hint as to its nature.

Fig. 6.—Case 7. Demonstration of the cecum situated in the upper midabdomen is diagnostic of malrotation. The sharp angulation in the cecum was found at operation to be caused by a duodenocecal band.

*Comment.*—This patient's rapid onset of symptoms and subsequent demise illustrates vividly how quickly

the newborn infant with intestinal obstruction can progress to bowel strangulation and how important is early recognition of such conditions in the newborn infant.

CASE 7.—P. K. H. (No. 49315), a female infant, 3 years old at the time of operation, was first seen at the age of 2 years because of recurrent attacks of severe abdominal pain during which she cried and straightened out her legs. These had been relieved at home by enemas. The infant was observed briefly and was discharged as having an intussusception. Four months later she was readmitted with a history of acute abdominal pain with crying. She vomited once with each of several such episodes from which she sought relief by assuming the knee-chest position. Enemas seemed to relieve the pain, and mucus was noted in the stools after each attack. Complete relief was obtained between attacks. Physical examination upon admission was unremarkable, and a barium enema revealed that the cecum pointed left and was situated in the upper mid-abdomen. The infant was discharged several days later with a diagnosis of malrotation of the gut. Three months later she was admitted for the third time with similar complaints. At this time a mass was felt in the epigastrium, disappearing with palpation, which was thought by one observer possibly to represent an epigastric hernia. She was discharged four days later after obtaining complete relief of symptoms from enemas. On Sept. 16, 1950, nine months after her first admission, this girl was admitted for elective exploration. After a right rectus incision, the cecum presented in the wound. There was venous stasis of the right colon and the entire small bowel with dilatation of the veins in the mesentery to three or four times normal size. Lymphatic stasis had dilated lymphatic channels to about 2 mm. in diameter, and the mesentery appeared as if milk had been injected between the leaves. The cause of the stasis was a volvulus of one and one-half turns of the entire small bowel about a mesenteric pedicle.

The second jejunal loop was held within the pelvis by a large lymphogenous cyst about 10 cm. in diameter which gave a dumbbell appearance within the leaves of the mesentery as the jejunum passed over it. It was believed to be the result, rather than the cause, of the child's symptoms though it would have served to maintain a volvulus, once created. The volvulus was reduced with complete relief of stasis. An avascular duodenocecal band was divided, placing the cecum in the left upper quadrant. The cyst was removed and the surfaces peritonealized. It was not possible to fix the small bowel posteriorly, for the mesentery was too short. The duodenum lay entirely on the right, there being no ligament of Treitz. The bowel was returned to the abdomen with the colon lying on the left, and the small bowel on the right. The patient's postoperative course was uneventful. Pathologic examination of the cyst removed at operation confirmed its lymphatic nature. Except for two admissions for gastroenteritis associated with upper respiratory infections in November and December, 1952, this girl has remained well since operation.

*Comment.*—The only previous report of a cyst associated with an anomaly of rotation or fixation which was found in a review of the literature was Hunter's[24] case, and there the cyst was of enterogenous origin and seemed to be the cause of the anomaly described. Here, however, the cyst was of lymphatic origin and arose apparently because of stasis incident to a volvulus which had its basis in a rudimentary small bowel mesentery. The present case is therefore believed to be the first reported instance of a lymphatic cyst associated with malrotation of the gut.

CASE 8.—D. S. (No. 213-360), a 14-hour-old premature female infant, was admitted Jan. 8, 1953, from another hospital because of an omphalocele and cyanosis out of oxygen. Physical examination revealed a large mass of viscera which lay outside the abdominal wall and was covered by a filmy sac. The omphalocele protruded from a 2 cm. diameter orifice inferior to the umbilicus. The liver was thought to lie within the abdomen. Operation was performed shortly after admission and a thin sac was dissected with difficulty from the bowel loops. Complete nonrotation of the colon was found with a duodenocecal band obstructing the duodenum. It was impossible to return the bowel to the abdomen, and 30 cm. of small bowel was resected and primary end-to-end anastomosis was performed. This allowed the bowel to be returned to the small abdomen which was closed with through-and-through sutures. The patient was in very poor condition throughout surgery, remained so postoperatively, and died about midnight the day of operation. Following postmortem examination, the final diagnoses were omphalocele complicated by chronic peritonitis and intestinal obstruction, an obstruction above the level of the anastomosis owing to kinking associated with peritonitis, malrotation of the colon, and prematurity.

CASE 9.—J. S. (No. 76334), a 3-day-old male infant, was admitted June 26, 1949, because of failure to retain formula feedings. The details of the immediate post-partum course were unknown to the parents. Physical examination was within normal limits as were the routine laboratory data. The infant continued to vomit most feedings after admission. Barium meal demonstrated three-hour gastric retention. The second part of the duodenum turned to the left. Barium enema showed that a colon loop at the hepatic flexure turned back on itself toward the duodenum and was thought to indicate a congenital band between the duodenum and colon. Six days after admission exploration was carried out, and the stomach was found to be slightly dilated. The entire right colon had no posterior fixation to the lateral colic gutter. Instead it hung on a rather long mesentery, the most proximal posterior fixation being at the hepatic flexure where a peritoneal band overlay the junction of the second and third parts of the duodenum. The band was divided; the rest of the abdomen was found to be normal. The abdomen was closed. The postoperative course was uneventful.

*Comment.*—Again the observation that where there is failure of normal mesenteric fixation abnormal peritoneal attachments are likely to occur is well illustrated. Here the primary anomaly was simply deficient posterior fixation of the right colon, but it gave rise to abnormal fixation obstructing the duodenum.

### TREATMENT

Not all patients who have radiologically demonstrable anomalies of intestinal rotation or mesenteric fixation require surgical treatment. Surgical treatment is not indicated in cases which are asymptomatic or where symptoms are of a minor order. It should be offered to those patients in whom there appears to be a reasonable chance of relieving distressing symptomatology. It is essential in those cases showing intestinal obstruction. Though certain procedures are discussed below in reference to particular anomalies, the procedure which can be performed in a given case may be modified by the condition of the patient or the findings within the abdomen. In reviewing the older literature it is apparent that the higher mortality rates obtained in dealing with these anomalies came not so much from

technically inferior procedures but rather from inadequate supportive treatment. In the patient who presents with acute intestinal obstruction, with or without signs of strangulation, it is much better to delay operation until the blood volume and fluid and electrolylyte status can be restored to more nearly normal levels than to attempt major surgery in the debilitated. Appropriate antibiotics should be given, and in the neonatal patient the administration of vitamin K preoperatively is essential.[14]

Treatment of anomalies of the first stage of rotation (i.e., those rare cases in which there is extroversion of the cloaca) is not discussed in the literature. Apparently infants with these gross defects are felt to have anomalies incompatible with life. Certainly this is true of the infant in Case 1 in the present series. Untreated, such patients usually succumb to an ascending pyelonephritis.[36]

Anomalies of the second stage of rotation require different procedures according to the type of anomaly involved. Before Ladd evolved the procedure which bears his name, various types of gastroenterostomies were used which produced rather poor results. His procedure involving division of obstructing duodenocolic bands and the mobilization of the cecum into the left side of the abdomen has become the standard procedure for the treatment of malrotation. The fact that it is a closed procedure, its simplicity, and the speed and safety with which it can be performed have all contributed to its general acceptance. However, Ladd[18] emphasized the necessity of making an incision which would provide adequate exposure and, especially, the necessity of removing the midgut loop from the abdomen in determining the exact nature of an anomaly at operation. Others have since found it desirable in instances of a rudimentary mesentery, where the length of the mesentery permits it, to fix the small bowel posteriorly with suitably placed sutures. In volvulus of the entire midgut loop surgical fixation posteriorly seems obligatory.[32] Where malrotation is associated with omphalocele, the immediate repair of the latter is essential, if only to cover the herniated viscera with undermined skin flaps from the adjacent abdominal wall. At operation for omphalocele, the possibility of a malrotation should be looked for because of the frequent association of these two anomalies.[14]

Anomalies of reversed rotation present entirely different problems at operation, and other procedures have been employed. Truesdale[11] was able to relieve obstruction permanently in one case of retroposition of the transverse colon by simply dilating the tunnel of small bowel mesentery through which the colon passed, while in another case a bowel resection was performed as a part of the procedure for bowel carcinoma. Today it seems that division of the retrodisplaced colon and primary end-to-end anastomosis might be the most desirable procedure. The treatment of paraduodenal hernia is operative reduction and obliteration of the sac. Because of the bowel distention commonly associated with such anomalies this may be technically difficult. While the opening of the sac and decompression of the incarcerated bowel is a satisfactory approach to

the problem, extreme care must be taken that the vessels lying in the free edge of the sac are not injured. Following reduction of the hernia, resection of the sac and closure of the orifice will prevent recurrence.[1, 14] This procedure has been combined with resection of a Meckel's diverticulum and small bowel in one case.[33] Duodenum inversum is an interesting and uncommon anomaly which is asymptomatic and requires no treatment.[34]

As has been noted previously, in the third stage of rotation varying degrees of incomplete fixation of the right colon or ileocolic segment may occasionally result in volvulus. In such cases, after reduction of the volvulus and exploration of the abdomen, surgical fixation posteriorly of the affected segment of bowel is indicated to prevent recurrence. This has been found to give lasting relief of symptoms.[10] Going now to the other end of the midgut loop, it has been found in the few reported cases of anomalous fixation of the duodenum in which obstruction resulted that division of the obstructing peritoneal folds was sufficient to relieve the obstruction.[23]

SUMMARY

1. Anomalies of intestinal rotation and mesenteric fixation are discussed, and nine cases are reported of patients who were treated at the Raymond Blank Memorial Hospital for Children from 1947 to 1953.

2. The history, incidence, and embryology of these conditions are briefly reviewed.

3. These anomalies are discussed in detail according to the classification of Dott, with the addition of paraduodenal hernias to his classification in the light of more recent thinking on the subject.

4. The fact that many congenital anomalies of intestinal disposition which present widely divergent appearances at operation have a common pathogenesis is emphasized.

5. Indications for surgical intervention in patients with such anomalies are enumerated, and accepted surgical procedures for their management are discussed.

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# Comments on Current Literature

## ENCEPHALOMYELITIS

ACUTE disseminated encephalomyelitis represents a poorly understood clinical syndrome which is associated not uncommonly with an acute febrile illness often of the exanthematous type, with Jennerian vaccination or other prophylactic inoculations, and more rarely associated with metabolic abnormalities such as acute porphyria.

Pertinent to this subject is an interesting article in the April, 1954, issue of the *Annals of Internal Medicine*[1] by Henry G. Miller and James L. Gibbons of England, which reports three unusual cases of recurrent encephalomyelitis in siblings from a single family, who ranged in age from 11 to 14 years. The authors had the unusual opportunity of studying twelve encephalomyelitic episodes in these three children. Ten of these episodes followed ordinary infections of the upper respiratory tract, such as tonsillitis and coryza. From a brief review of the literature the authors were impressed with the comparative rarity of true recurrence of encephalomyelitic illness on this basis. In their unusual experience with this particular family, Miller and Gibbons were able to obtain for study and comparison very complete case histories.

The first patient, eldest of the three siblings, a 14-year-old boy, experienced during a period of eight months six episodes of encephalomyelitis following upper respiratory infections. The second patient, a boy of 12 years, had four such episodes in a course of seven months, two of which were associated with upper respiratory infections. The third patient, a 13-year-old sister, experienced two encephalitic illnesses over a six weeks' period, both of which followed infections of the upper respiratory tract.

In a consideration of the varied and rather bizarre symptoms presented by these three siblings, the authors noted a fairly consistent clinical pattern and described the essential clinical manifestations as being initiated by an "onset (usually a few days after an apparently nonspecific infection of the upper respiratory tract) of headache, vertigo, ataxia, and drowsiness or mental confusion, proceeding to stupor with hypotonia and loss of deep reflexes. Variable and transient internal and external ophthalmoplegias were not uncommon. In the more severe episodes stupor deepened to coma, sphincter disturbances occurred, and the plantar responses became extensor. Fever and meningism were inconstant and spinal fluid changes inconspicuous. Nystagmus, diplopia, dysarthria, dysphagia, disorientation and disturbances of mood and behavior were all seen in some cases during recovery, but residual disturbances of emotional life and conduct, like electroencephalographic changes, tended to be short-lived."

Several interesting points are apparent on review of the individual clinical summaries of these three patients. The first of these is trauma: All three of these children had suffered a head injury at some previous date, four months, two years, and eight years, respectively, prior to the initial encephalitic episode. In consequence, trauma to the central nervous system as a possible predisposing factor in these unusual occurrences of encephalomyelitis had to be considered. However, since the type of encephalomyelitis observed in these patients has been known to occur in the absence of any craniocerebral trauma, the authors

tend to lay more stress on diathetic familial predisposition to the encephalitic type of response in attempting to account for the central nervous system manifestations observed in the siblings in question. The consistent lack of abnormal findings in the cerebrospinal fluid seems significant. The transient, although apparently definite, changes observed in the electroencephalographic pattern suggest a pathologic process of reversible nature. All attempts to isolate a viral agent by animal inoculations of spinal fluid were unsuccessful. Disturbances in metabolism were considered as a possible explanation for the encephalitic episodes, and porphyria, at least, was excluded. Various biochemical investigations were undertaken and all results were negative, the determinations being within normal limits.

That the pathogenesis involved might be explained on the basis of anaphylactic hypersensitivity, possibly associated with constitutional diathesis, was suggested by the fact that the authors observed clinical improvement in five of the twelve episodes of encephalomyelitis following the use of ACTH. Another approach, particularly from the standpoint of prophylaxis, includes the use of antihistaminic drugs, suggested on the basis of animal investigations in which allergic-type encephalomyelitis has been produced experimentally by repeated injection of heterologous tissue elements.

This presentation by Miller and Gibbons constitutes an interesting clinical study of recurrent encephalomyelitis in siblings, a clinical syndrome which is not understood thoroughly and for which definitive treatment is still not available. The remarkable familial incidence of encephalomyelitis in this instance is worthy of special note.

RUSSELL J. BLATTNER

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# Correspondence

Dear Dr. Veeder:

It was gratifying to read in the Editor's Column in the June, 1954, issue of the JOURNAL the discussion of our paper on cortisone in the prevention of rheumatic carditis. We are in full agreement with the views expressed.

We are aware of the pitfalls of generalizing from a small series of cases, but we wish to stress that the arbitrary dosage schedule of the study by the International Group was not adequate. The results of that study are probably valid for that fixed dosage schedule. Our results are confirmed by those of Greenman and associates.* It is suggested that a study similar to that of the Cooperative Group but using high dosage (300-500 mg. for six to eight weeks) be instituted. This would be the only way to see whether *early, intensive* treatment prevents residual cardiac damage.

IRVING G. KROOP, M.D.

*Greenman, L., Weigand, F. A., and Danowski, T. S.: Prevention of Cardiac Abnormalities in Acute Rheumatic Carditis, J. Clin. Invest. 32:572, 1953.

# News and Notes

Dr. Henry J. Gerstenberger of Cleveland died June 24, 1954, of heart disease, aged 73. After his graduation from Western Reserve Medical School in 1903, he interned and studied pediatrics for several years in Germany. Returning to Cleveland he became Professor of Pediatrics in the medical school and Medical Director of the Babies Dispensary and Hospital. He organized municipal infant welfare clinics in close affiliation with the hospital, and the infant welfare work in Cleveland became an outstanding pioneer development in the period 1910 to 1920. He worked out the first one-formula infant food, S-M-A. He was a member of a number of medical societies, including the American Pediatric Society and the Deutsche Gesellschaft für Kinderheilkunde.

Dr. Alex J. Steigman, Professor of Child Health, has been appointed Chairman of the Department of Pediatrics at the University of Louisville School of Medicine.

The 1954 annual convention of the **National Society for Crippled Children** will be held Nov. 3 to 5, 1954, at the Hotel Statler, Boston, Mass.

In a letter to state and territorial health officers, dated May 21, the **U. S. Public Health Service** restated the policy dealing with the distribution of *gamma globulin for the prophylaxis of measles and infectious hepatitis.* The letter states that the supply is adequate to meet all foreseeable requirements and that there is no restriction from the standpoint of the Office of Defense Mobilization or the Public Health Service in providing the material to state and territorial health officers. The state or territory is free to regulate the distribution within its area as it sees fit; however, limitations are not indicated if they are based on assumed inadequacy of supply.

The **New York Academy of Medicine** will hold its twenty-seventh annual graduate fortnight Oct. 18 to 29, 1954. The subject is "Infections and Their Management." The program will consist of twenty evening lectures, six morning panel meetings, and ten hospital clinics. Program and registration card may be obtained from Robert L. Craig, M.D., 2 East 103rd St., New York 29, N. Y.

A post-graduate course in Pediatric Allergy, under the direction of Bret Ratner, M.D., is offered by the **New York Medical College,** Nov. 3, 1954, to May 25, 1955. Applicants must be certified in pediatrics

or have the requirements for certification. Enrollment limited. For details apply to Office of the Dean, Fifth Avenue at 106th Street, New York 29, N. Y.

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A three-day International Symposium on the Hypophyseal Growth Hormone, Its Nature and Actions is being sponsored by the **Henry Ford Hospital** and the **Edsel B. Ford Institute for Medical Research.** The Symposium will be held in the New Clinic Building Auditorium of the Henry Ford Hospital, Oct. 27 to 29, 1954. Formal presentations and discussions will cover the following aspects of growth hormone investigation: bioassay, preparation, and physico-chemical properties of growth hormone; effects of growth hormone on certain structures such as the mammary gland, skeletal system, connective tissue, islets of Langerhans, kidneys, gastrointestinal tract, and tissue cultures; growth hormone and energy sources; the effect of growth hormone on cellular systems; the influence of growth hormone on lactation; and its metabolic effects in man. Interested persons should write the Program Committee, Henry Ford Hospital, Detroit 2, Michigan. Invitations will be sent to as many persons as possible.

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The Pediatric Staff of the **Cook County Hospital** announced that the Sixth Annual Morris Lamm Blatt Memorial Fund lecture will be given Oct. 18, 1954. Dr. Otto Glasser, Chairman of the Department of Biophysics of the Cleveland Clinic, will speak on "Medical Physics, and the Neo-Atomic Age." The lecture will be presented at 8:30 P.M. in the Medical Amphitheatre of the Cook County Hospital.

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A training program for personnel concerned with the *care of cerebral palsy children* under the direction of Dr. Luigi Luzzatti will begin at **Children's Hospital, San Francisco,** September, 1954. This was made possible by a grant received from the United Cerebral Palsy Associations. For the coming academic year funds are available for a maximum of six students. There will be two courses of five months' duration beginning on Sept. 1, 1954, and Feb. 1, 1955. Students will receive a stipend of $750 during their training program. Information and application forms may be obtained from Miss Helen B. Holodnak, Children's Hospital, 3700 California St., San Francisco 18, California.

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The **Memorial Center for Cancer and Allied Diseases** announces the establishment of a second *Fellowship* in *Pediatric Oncology.* The pediatric residencies held under these fellowships are approved for partial credit by the American Board of Pediatrics. Appointments are made July 1 and January 1 for six or twelve months. The thirty-bed pediatric service is exclusively for the study and treatment of children with cancer and related diseases. Salary: $3,600 annually plus maintenance. For further information communicate with: Director, Pediatric Service, Memorial Center, 444 E. 68th St., New York 21, N. Y.

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The **National Foundation for Infantile Paralysis** offers for the first time one-year clinical fellowships in the management of poliomyelitis. The purpose of the fellowships is to train physicians in the various aspects of the total care of the poliomyelitis patient. Applicants for fellowships must be United States citizens (or applicants for citizenship), and must have completed at least one year of internship in a hospital approved by the Council on Medical Education and Hospitals of the American Medical Association. Selection will be made on a competitive basis. Stipends will range from $300 to $400 a month depending upon marital status and number of dependents. Before applying for a fellowship, the candidate should arrange for a program of full-time study at any institution having suitable facilities for this type of training. Applications for fellowships received by September 1 will be considered in November; those received by December 1 will be considered in February; those submitted by March 1 will be considered in May. For application forms and further information, address the National Foundation for Infantile Paralysis, Division of Professional Education, 120 Broadway, New York 5, N. Y.

# Book Reviews

**Seventy-five Years of Medical Progress.** Edited by Louis H. Bauer, M.D., Philadelphia, 1954, Lea & Febiger, 279 pages. Price $4.00.

A collection of papers presented by specialists in various fields at the First Western Hemisphere Conference of the World Medical Association in Richmond in 1953. The theme was the commemoration of seventy-five years of medical progress, and nineteen specialists and a general practitioner presented discussions of the progress that had been made in their particular fields in the last seventy-five years. Dr. Louis H. Bauer, Secretary-General of the World Medical Association, writes a Foreword.

We would like to end the review of the book with this statement of its contents, but the publisher urges that it be reviewed *critically*. It contains one of the most heterogeneous discussions of a theme or subject that we have come across. Some of the contributors obviously realized that an attempt to present in ten to twelve pages a comprehensive picture of the developments in knowledge in their particular field over a period of seventy-five years was futile, and quite avoided a general discussion. Dr. Bartemeier, for example, begins with the impact of World War II on psychiatry, or vice versa, and goes on to discuss the importance of postgraduate instruction in psychosomatic medicine. Freud is not mentioned. Some in their attempt to cover their field have brought in the names of so many men who have made significant contributions that the reader is left with the feeling of having read an index column. In some the discussion of the developments in a particular field of their specialty is so sketchy that it quite fails to have any value. A somewhat amazing thing in discussions of the "progress of knowledge" is the way several have included the "Boards." In his discussion of otolaryngology, Dr. Lempert even brings in the names of the original Board members, and the Boards are mentioned in several other discussions. While the Boards have had a decided influence on medical education, practice, and the hospital care of patients, it is difficult for the reviewer to see how they have added to medical knowledge. This was never their function or purpose. Dr. Irvine McQuarrie discusses pediatric progress in a very general way. How he could have done otherwise in ten pages is hard to see, as it would take a text the size of the entire book to discuss the progress of pediatrics in the last seventy-five years from a historical and critical standpoint.

There is another matter which concerns the make-up of the book. Each chapter is faced by a full-page picture of the author. It was pleasant to see the faces of some old acquaintances whom one rarely meets in the present era of meetings segregated by special interests, and to note Dr. X is getting a little bald and Dr. Y a little gray. Further, to see what some men look like whom we only know by name and reputation. However, we could not help feeling that in a text on seventy-five years of medical progress it would have been more in keeping with the theme if for pathology, for example, a portrait of Virchow or Pasteur had been used, or one of Czerny or Jacobi for pediatrics, and so on for the entire group. This is not meant as a reflection or criticism on those who took part in the discussion but of those responsible for the make-up of the book.

The great shortcoming of the book is its attempt to cover a big and interesting field in short sketchy discussions which are very uneven in quality and content.

B. S. V.

**Antibiotika-Fibel.** Dr. Albert M. Walter and Prof. Dr. Ludwig Heilmeyer, Stuttgart, 1954, Georg Thieme Verlag, 813 pages. Price $18.80. (Intercontinental Medical Book Corp., New York 16.)

There is nothing in English quite comparable to this extensive discussion of therapy with the sulfonamides and antibiotics by members of the University Medical Clinic in Freiburg. The first part of the text is an excellent general discussion of the sulfonamides and the various antibiotics, and of the bacteriological tests before and during therapy. Four-fifths of the book is devoted to their clinical use. The discussion is by systems, as tropical diseases, infections of the respiratory tract, meningeal infections,

etc. The material is well arranged and thoroughly cross-referenced. Each disease and chapter is followed by an extensive world-wide bibliography. Both the study of the material and its compilation and arrangement reflect a tremendous task. Even with a subject that is constantly changing, the book should be a most valuable addition to the hospital and clinic library, and should save many hours of "literature hunting" when a moot point or question comes up. The reviewer was particularly impressed by the excellence of the format.

**Handbook for Diabetic Children.** Alfred E. Fischer, M.D., and Dorothea L. Horstmann. Intercontinental Medical Book Corp., New York, 1954, 64 pages. Price $1.75.

A very worth-while inexpensive handbook which can be easily understood by both the older diabetic child and his parents. Explains the subject of diabetes mellitus and the approach to treatment simply and yet fully and allows enough leeway for variation, depending on the individual doctor's concepts.

W. G. K.

**Die Narkose.** H. Killian and H. Weese, Stuttgard, 1954, Georg Thieme Verlag, and Intercontinental Medical Book Corp., New York, N. Y., 1003 pages. Price $40.50.

This book covers very completely the general subject of anesthesia in its twelve chapters and one thousand pages. In sequence it considers the historical development of anesthesia, its theoretical aspects, the action of narcotic drugs on different tissues and organs, techniques of administration, and clinical aspects. Choice of method and of drug is thoroughly discussed, as are complications and methods of resuscitation. It should serve as a very valuable reference book for anesthesiologists, surgeons, physiologists, and pharmacologists.

A. F. H.

**The Long-Term Prognosis for Prematurely Born Children.** Ingvar Alm. Supplement 94 to Acta Paediatrica, Uppsala, 1954, Almqvist & Wiksells, 116 pages. Price 15 Swedish Cr.

Alm reports on a study of 999 male premature infants, 2,500 grams or less at birth, born in Stockholm in the years 1902 to 1921, with a control group of 1,002 infants weighing 2,760 to 3,750 grams at birth. There was a higher mortality rate in the first months of life for the premature infants, due mainly to infectious disease. After two years the mortality rate evened out. At 20 years of age there was a statistically significant difference between the two groups in height and weight, the premature group being lower. The incidence of those able to do their military service was the same for the two groups, and the duty performance was equal. As to social adaptations no statistically significant or probable differences between the two groups was found. In the majority of respects the premature group equalled the controls.

**Gesundheit durch Krankheit.** Dr. H.-J. Flechtner, 1954, Düsseldorf, Econ-Verlag GMBH, 346 pages.

This volume with the paradoxical title "Health Through Sickness," is a semi-popular discussion of the problems of immunity. It discusses the origin of infectious diseases, their attack on the organism, and the development of protection through immunity. The author finally reaches the conclusion that the prevention of disease through artificial immunization is the desirable goal. There is nothing particularly new to physicians in the book.

**The Causes and Treatment of Backwardness.** Sir Cyril Burt, New York, 1953, Philosophical Library, Inc., 128 pages. Price $3.75.

A discussion of backwardness by a well-known psychologist. The subject is considered from the educational and teacher's standpoint rather than the medical. After a consideration of the environmental and development causes of backwardness and intellectual characteristics, the author discusses educational problems and methods.

**Disease of the Retina.** Herman Elwyn, M.D., New York, 1953, The Blakiston Company, Inc., 713 pages. Price $12.00.

A second revised edition. Because of the increasing incidence of and interest in retrolental fibroplasia, retinal lesions are of more interest to the pediatrician today than in previous years. The book is thoroughly illustrated with twenty color plates.

# Editor's Column

## SOCIAL MEDICINE

DO NOT be disturbed; this is not a discussion of socialized medicine.

To readers of the JOURNAL who are interested in medicine from a broad standpoint and not simply in the diagnosis and treatment of disease, and in particular to those who have the responsibility for medical teaching and education, we recommend a recently published book *The Meaning of Social Medicine** by Dr. Iago Galdston. The author served for five years as secretary and administrative officer of the Committee on Medicine and the Changing Order of the New York Academy of Medicine, whose excellent studies and reports have been the subject of comment a number of times in the JOURNAL.

Social medicine is a term that is frequently encountered in British medical literature and rather infrequently in American. It is a difficult term to define briefly or with exactness, as it means somewhat different things to physicians with different interests, although it contains something common to all. It is not socialized medicine, as this is essentially a modality based on a political rather than a medical philosophy. Nor is it public health or preventive medicine as these presently exist. Further, it is not the addition of the social sciences to the medical sciences. Rather it expresses a philosophy that medicine as it exists today, as Galdston states it, has "failed in the elimination of disease and in the promotion of health," and hence a new approach, or medical philosophy, is needed. In Great Britain this philosophy has led to the development of Institutes of Social Medicine in a number of universities, and it is the philosophy behind the appointment of outstanding pediatricians, such as Spence and Moncrieff, to professorships of child health in British medical schools.

Galdston finds the origin of the concept of social medicine in the history of medicine itself, and cites from the dissenters to the viewpoint that an etiological philosophy is the answer to all medical problems. He stresses, for example, the epidemic constitution—the why in great pandemics when all are exposed some contract the specific disease and others do not. One of the most interesting chapters is the discussion of mortality and morbidity. The decrease in mortality in the last fifty years, with its corollary, the increase in longevity, has been emphasized time and again as proof of the value of current medicine. Galdston points out that we must "distinguish between a reduced mortality rate and improvement in health and well-being." While the development of vaccines, antibiotics, etc., has brought about enormous achievements in treating disease, they do not in themselves promote health or well-being. He gives some estimates of the prevalance of conditions causing ill health, and quotes a calculation that one-sixth of

*_The Meaning of Social Medicine_, by Iago Galdston, M.D. A Commonwealth Fund Book published in 1954 by the Harvard University Press, Cambridge, Mass. Price $2.75

our population, some 25,000,000 individuals, suffers from chronic diseases, and that over half of these are under 45 years of age. He asks if this is not a challenge to "curative medicine" which is "so eager and so competent to treat and remedy a man's illness, but so little concerned with his ill health."

Social medicine in no way belittles the tremendous scientific developments of recent years and the vast progress that has been made in the field of nutrition and in the treatment of disease. These have been developed on the etiological concept or philosophy of medicine which has dominated medical thought and education from its earliest beginnings. This philosophy of medicine, the advocates of social medicine feel, has failed to meet man's needs for health, and hence should be replaced by a concept or philosophy of environmental medicine into which curative medicine would fit as a part.

To bring about this change in medical philosophy, that is, from medicine as it exists and is taught today, implies fundamental changes in medical education. Some of the British essays into the field of social medicine have not been so successful. For example, the Institute of Social Medicine at Oxford has been closed. There have been a number of vague gropings, reflecting a changing philosophy in education, in a few of our own medical schools in recent years, which fit into the concept of social medicine. The term "social medicine," however, has been avoided, probably because of its similarity to the term "socialized medicine" which provokes an immediate emotional reaction in many physicians, negating calm thinking.

We wish Galdston had elaborated on his brief statement, "Knowingly or otherwise, pediatrics is a specialty conceived in the spirit of social medicine." Not only in England—he refers to the work of Sir James Spence whose recent death is a heavy loss to pediatrics—but in the United States pediatrics is the outstanding example of what is meant by social medicine. Pediatrics, however, was not conceived with this philosophy in mind, but it was an attitude or concept that gradually grew and developed from 1910 to 1940 which looked upon pediatrics as primarily concerned with the child and not disease. We have the feeling that this concept of pediatrics has been slipping a little in the past ten years, coincident with the rapid development of pediatric clinics in our medical schools based on the German pattern of forty to fifty years ago. This, however, is another matter, and whether pediatrics is retreating to a position which is concerned chiefly with the diagnosis and treatment of disease, a position which will eventually relegate it to a subdepartment of internal medicine and from which it was rescued not so many years ago by the concept of pediatrics being concerned with the "total child," is a theme the editor has in mind to discuss at some future time.

Whether or not you agree with Galdston's contentions, and the philosophy of social medicine as contrasted with a philosophy based on the diagnosis and treatment of specific diseases, we are certain our readers will find this short book an interesting and thought-provoking discussion. We need something once in a while to disturb our complacency.

## CIRRHOSIS OF THE LIVER IN INFANTS

THE *Indian Journal of Child Health* for March, 1954, page 157, contains an interesting letter from a physician in Dandar, Bombay, four of whose children died of cirrhosis of the liver. In the first child the diagnosis was made at 5 months and in the subsequent cases between the second and third months of life.

The first child received breast milk at irregular intervals; the second child received breast milk and oster milk, a dried, low fat, milk powder; the remaining two were fed on breast milk and cow's milk. Diarrhea, resistant to treatment, was a prominent symptom. The children were lethargic and motor development was delayed. The liver and spleen were greatly enlarged and hard. A sweetish odor to the breath was present in all four children.

Treatment with crude liver injections and Jammi's liver cure* was ineffective even when started early in life (at 1½ months). The mother received Jammi's liver cure during the third and fourth pregnancies but this had no apparent effect. The children died from intercurrent infections at ages 11 months, 1 year, 15 months, and 11 months, respectively.

*Jammi's liver cure contains, among other ingredients, zinc, ferrous, and ferric oxides, calcium and sodium salts, astringent, diuretic and antipyretic drugs.

The parents are strict vegetarians. There is no Rh incompatibility, and the Wassermann reactions have been negative. The disease is known to be familial. Presumably the defect is on the maternal side since, in times where there were families with two wives, the children of one wife could have the disease while the children of the other wife remained free.

The parents were advised against having more children but they persisted and subsequently produced two normal children. Therapy was based on the assumption that the form of cirrhosis of the liver prevalent in infants in India is produced by a maternal diet which is deficient in protein. Throughout her two last pregnancies the mother received protein hydrolysate with methionine and choline. After birth the babies were not nursed at the breast but were given Hi-Pro, a milk powder of high protein content, until the third month, and Hi-Pro mixed with oster milk thereafter. In addition the children received vitamins C and K and Vi-Syneral. At the time of writing the children were 3½ years and 11½ months old, respectively, and were well.

H. B.